ES

#3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION OF: Juan C. Colberg *et al.* : Examiner: To Be Assigned
APPLICATION NO.: 10/006,279 :
FILING DATE: 12/04/2001 :
TITLE: COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS :

Commissioner for Patents
Washington, DC 20231

Sir:

Petition To Establish Prior Receipt in the USPTO of The Missing Page In A Non-Provisional Patent Application Pursuant To 37 C.F.R. 1.53(e)

Pursuant to 37 C.F.R. §1.53(e), Attorney for Applicants hereby petitions the Commissioner for Patents to establish prior receipt in the USPTO of the allegedly missing page 12 in the above-identified non-provisional patent application. This petition is filed as a response to the Notice of omitted items mailed January 25, 2002, which response is due on March 25, 2002. Accordingly, this response is filed timely. Attorney for Applicants hereby asserts that the allegedly missing specification page 12 was submitted at the time of non-provisional filing of December 4, 2001.

This petition is accompanied by sufficient evidence under 37 C.F.R. §1.181(b) to establish Applicants' entitlement of the December 4, 2001 non-provisional filing date. The submitted evidence is a copy of the date-stamped postcard receipt to establish prior receipt in the USPTO of the allegedly missing page 12 of the non-provisional specification, along with a copy of the submitted non-provisional specification. In the postcard, it is stated that on December 4, 2001, a total of 38 pages of the non-provisional specification, which includes 32 specification pages (including the allegedly missing page 12 at issue) were submitted. As further evidence, Applicants' Attorney hereby submits a copy of the priority provisional specification No 60/251,014 filed on December 4, 2000. The Commissioner's attention is directed to page 11, lines 22-26, of the provisional specification, which provides support for the allegedly missing page 12 of

the non-provisional specification. Applicants' Attorney hereby submits that the copy of both provisional and non-provisional specifications and the copy of the date-stamped postcard receipt establish prior receipt in the USPTO of the allegedly missing page 12 of the above identified non-provisional specification.

A petition fee set forth in 37 C.F.R. §1.17(h) accompanies this petition. Authorization is hereby provided to charge the amount of $130.00 as stated under 37 C.F.R. §1.17, as well as any additional fees required, or to credit any overpayment to Deposit Account No. 16-1445. Applicants' Attorney hereby requests that the fee be refunded upon determination that the allegedly missing page 12 was received by the USPTO on the December 4, 2001 non-provisional filing date.

A copy of the notice of omitted item accompanies this petition.

Respectfully submitted,

Date: March 25 '02

Elsa Djuardi
Reg. No. 45,963
Attorney for Applicants

Date Mailed: 10/24/01 Express Mail No. ---------

Application No. 60/251,014 Docket No. PC10862 By EDJ:mdd

Application of Juan Colberg et al. Filing Date 4December 2000

Entitled Coupling Process and Intermediates Useful for Preparing Cephalosporins

EDJ

The following, has been received in the United States Patent and Trademark Office and stamped hereon:

- ☐ Application Transmittal *Type:* _____
- ☐ Specification _____ *pages*
- ☐ Claims _____ *pages*
- ☐ Abstract _____ *pages*
- ☐ Drawing(s) _____ *sheets*
- ☐ Declaration with Power of Attorney
- ☐ Priority Document
- ☐ Disclosure Statement
- ☐ Form PTO-FB-A820 (Citation List) _____ References
- ☐ Sequence Submission (☐ Computer Readable Copy, ☐ Paper copy ☐ Identity Statement)
- ☐ Copy of Notice to File Missing Parts, Cover Letter
- ☐ Amendment
- ☐ Reply
- ☐ _____
- ☐ _____

- ☐ Notice of Appeal
- ☐ Brief (3 copies)
- ☐ Issue Fee Transmittal
- ☐ Fee Address Indication Form
- ☐ Certificate of Correction
- ☐ Petition for Extension of Time *mos:* ____
- ☐ Fee Transmittal (2 copies)
- ☐ Associate Power of Attorney
- ☐ Petition for Expedited Issuance for Foreign Filing License
- ☐ Assignment & Recordation Cover Sheet
- ☒ ~~Amendment to Correct Inventorship~~
- ☐ _____
- ☐ _____

Date Mailed: November 02, 2001 Express Mail No. _____

Serial No. 60/251,014 Docket No. PC10862 By BFB

Application of Juan C. COLBERG Filing Date December 04, 2000

Entitled COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS

The following, has been received in the United States Patent and Trademark Office on the date stamped hereon:

- ☐ Application Transmittal *Type:*
- ☐ Specification *pages*
- ☐ Claims *pages*
- ☐ Abstract *pages*
- ☐ Drawing(s) *sheets*
- ☐ Declaration with Power of Attorney
- ☐ Priority Document
- ☐ Disclosure Statement
- ☐ Form PTO-FB-A820 (Citation List) References
- ☐ Sequence Submission (☐ Computer Readable Copy, ☐ Paper copy ☐ Identity Statement)
- ☐ Copy of Notice to File Missing Parts, Cover Letter
- ☐ Amendment
- ☐ Reply
- ☐ Notice of Appeal
- ☐ Brief (3 copies)
- ☐ Issue Fee Transmittal
- ☐ Fee Address Indication Form
- ☐ Certificate of Correction
- ☐ Petition for Extension of Time
- ☐ Fee Transmittal (2 copies)
- ☐ Associate Power of Attorney
- ☐ Petition for Expedited Issuance for Foreign Filing License
- ☒ Assignment & Recordation Cover Sheet

DEC 3 2001

Date Mailed: November 02, 200 Express Mail No. _____

Serial No. 60/251,014 Docket No. PC10862 By BFB

Application of Juan C. COLBERG et al. Filing Date December 04, 2000

Entitled COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS

The following, has been received in the United States Patent and Trademark Office on the date stamped hereon:

- ☐ Application Transmittal *Type:*
- ☐ Specification *pages*
- ☐ Claims *pages*
- ☐ Abstract *pages*
- ☐ Drawing(s) *sheets*
- ☐ Declaration with Power of Attorney
- ☐ Priority Document
- ☐ Disclosure Statement
- ☐ Form PTO-FB-A820 (Citation List) References
- ☐ Sequence Submission (☐ Computer Readable Copy, ☐ Paper copy ☐ Identity Statement)
- ☐ Copy of Notice to File Missing Parts, Cover Letter
- ☐ Amendment
- ☐ Reply

DEC 3 200

- ☐ Notice of Appeal
- ☐ Brief (3 copies)
- ☐ Issue Fee Transmittal
- ☐ Fee Address Indication Form
- ☐ Certificate of Correction
- ☐ Petition for Extension of Time
- ☐ Fee Transmittal (2 copies)
- ☐ Associate Power of Attorney
- ☐ Petition for Expedited Issuance for Foreign Filing License
- ☒ Assignment & Recordation Cover Sheet
- ☐
- ☐
- ☐

U.S.

MAILING REQUEST *PLEASE PRINT*

ORIGINATED BY: Bibi F. Bachu		DATE 11/02/01
BUILDING/FLOOR/STOP NO. 150/05/49	DEPT. CHG. NO. 88421	EXT. 573-7998

SHIP TO: *(Street Address and Phone # Required on Label)*

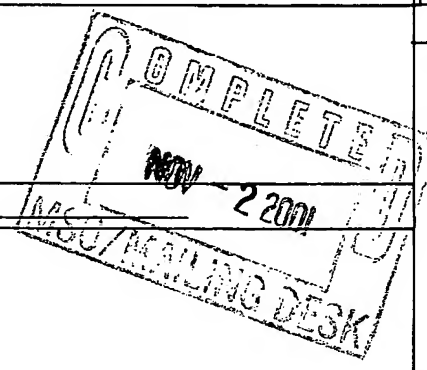
Honorable Commissioner of Patents and Trademarks
Washington, D,C,
Box Assignment

Zip Code

2	0	2	3	1					

SHIP-TO PHONE NUMBER: (212)573-7998
(Phone contact required for all two-day or next-day deliveries.)

QUANTITY	COMPLETE DESCRIPTION
1	Legal documents PC 10862



☐No Value ☐Insure For $ _____

Other (Please explain here)

International - Routing

☐International ☐Registered ☐Air Mail
Courier*
☐Other Explain *Customs forms will be provided by Shipping Dept. based on your complete description

Domestic Only – Routing

☐First Class ☐Insured ☐Messenger
☐Parcel Post (Third Class) ☐Registered ☐Truck
☐Book Rate(Fourth Class) ☐Certified ☐UPS

Domestic Only – Priority Options

☐Next Business Day ☐AM ☐PM
☐**Saturday Delivery Required.**
Not all areas are serviced. Call Ext. 7796 to confirm your destination.
☐USPS Express Mail Next Day (For Post Office Boxes Only)
☐Second Business Day
☒U.S. Postal Service Priority Mail

SPECIAL SERVICES

☐No Signature Required (Federal Express, Express Mail)
☐Bill Recipient/Third Party; Account #_____
☐Return Receipt (Certified, Registered, Express Mail, Priority Mail, Messenger)
☐Proof of Delivery (Fed Ex, DHL, U.P.S.)
☐Pick-up Only (Messenger or Truck)
☐Delivery & Pick-up (Messenger or Truck)
☐Hold at Messenger Center for Pre-Arranged Messenger/Courier Pickup
☐Other Explain_____

8385-1(12/95) 3B PF-MSO-01

EXD

Express Mail No. EL639814149US Docket No. PC10862 By EXD

Serial No. ~~NOT YET ASSIGNED~~ Filing Date CONCURRENTLY HEREWITH

Application of Juan C. Colberg

Entitled Coupling Process and Intermediates Useful for Preparing Cephalosporins

The following, due _____ in the U.S. Patent Office, has been received there on the date stamped hereon:

- ☒ Specification 26 pages
- ☒ Claims 5 pages
- ☒ Abstract 1 pages
- ☐ Drawing(s) ____ sheets
- ☐ Declaration with ☐ Power of Attorney
- ☐ Assignment & Recordation Cover Sheet
- ☐ Letter of Transmittal
- ☒ USPS Certificate of Mailing (Express Mail)
- ☐ Disclosure Statement ____ References
- ☐ Issue Fee Transmittal
- ☐ Fee Address Indication Form
- ☐ Affidavit ☐ Declaration ☐ Oath
- ☐ Certification 37 CFR 3.73(b)
- ☐ Notice of Appeal
- ☐ Amendment
- ☐ Brief (3 copies)
- ☐ Letter
- ☐ Petition for Extension of Time
- ☐ PTO-1390 (DO/EO/US) ____ pages
- ☐ Priority Document
- ☒ Provisional App. Cover Sheet
- ☒ _____
- ☐ _____
- ☐ _____

F

RECORDABLE

Date Mailed: 03/08/2002 Express Mail No. _____

Serial No. 60/251,014 Docket No. PC10862 By EDJ

Application of J. Colberg et al. Filing Date 12/04/2000

Entitled COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS

The following, has been received in the United States Patent and Trademark Office on the date stamped hereon:

- ☐ Application Transmittal *Type:* Utility
- ☐ Specification *pages*
- ☐ Claims *pages*
- ☐ Abstract *pages*
- ☐ Drawing(s) *sheets*
- ☐ Declaration with Power of Attorney
- ☐ Priority Document
- ☐ Disclosure Statement
- ☐ Form PTO-FB-A820 (Citation List) References
- ☐ Sequence Submission (☐ Computer Readable Copy, ☐ Paper copy ☐ Identity Statement)
- ☒ Copy of Notice to File Missing Parts, Cover Letter
- ☒ **Application Data Sheet (Supplemental)**
- ☐ Reply
- ☐ Notice of Appeal
- ☐ Brief (3 copies)
- ☐ Issue Fee Transmittal
- ☐ Fee Address Indication Form
- ☐ Certificate of Correction
- ☐ Petition for Extension of Time
- ☐ Fee Transmittal (2 copies)
- ☐ Associate Power of Attorney
- ☐ Petition for Expedited Issuance for Foreign Filing License
- ☐ Assignment & Recordation Cover Sheet
- ☒ **Provisional Cover Sheet**
- ☐
- ☐

(2)

Attorney Docket No.
PC10862

I hereby I certify that this correspondence is being deposited with the United States Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, Box Missing Parts, Washington, D.C. 20231 on this 8th day of March, 2002.

By _____
(Signature of person mailing)
Elsa Djuardi

(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: **J. Colberg et al..**	:	
APPLICATION NO. **60/251,014**	:	CUSTOMER CORRECTION BRANCH
FILING DATE: **12/04/2000**	:	ART UNIT: Not assigned
TITLE: **COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS**	:	
	:	

Box Missing Parts
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

RESPONSE TO NOTICE TO FILE MISSING REQUIREMENTS

This is a response to a Notice to File Missing Requirements under 35 U.S.C 37, mailed on January 25th, 2002, of a United States Provisional Application Serial No. 60/251,014. A supplemental data sheet and a provisional application cover sheet identifying city and foreign country of the residence of each inventor, along with a copy of the Notice to File Missing Requirements are enclosed. Authorization is hereby provided to charge the required fee, estimated to be $50.00, to Pfizer Deposit Account No. 16-1445.

Respectfully submitted,

Date: March 8'02

Elsa Djuardi
Attorney for Applicants
Reg. No. 45,963

Pfizer Inc
Patent Department, 20th Fl.
150 East 42nd Street
New York, NY 10017-5755
(212) 733 1417

Application Information

Application Number::	60/251,014
Filing Date::	12/04/2000
Application Type::	Provisional
Subject Matter::	Utility
Title::	COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS
Attorney Docket Number::	**PC10862**

Inventor Information

Inventor Authority Type::	INVENTOR
Primary Citizenship Country::	US
Given Name::	Juan
Family Name::	Colberg
City of Residence::	
State or Prov of Residence::	
Country of Residence::	
Street::	
City::	Norwich
State or Province::	CT
Postal or Zip Code::	
Inventor Authority Type::	INVENTOR
Primary CitizenshipCountry::	Italy
Given Name::	Maurizio
Family Name::	Zenoni
City of Residence::	
State or Prov of Residence::	
Country of Residence::	
Street::	
City::	MIlan
State or Province::	Italy
Postal or Zip Code::	
Country::	Italy
Inventor Authority Type::	INVENTOR
Primary CitizenshipCountry::	Italy
Given Name::	Giovanni
Family Name::	Fogliato
City of Residence::	

State or Prov of Residence::	
Country of Residence::	
Street::	
City::	Bergamo
State or Province::	Italy
Postal or Zip Code::	
Country::	Italy
Inventor Authority Type::	INVENTOR
Primary CitizenshipCountry::	Italy
Given Name::	Alessandro
Family Name::	Donadelli
City of Residence::	
State or Prov of Residence::	
Country of Residence::	
Street::	
City::	Lodi
State or Province::	Italy
Postal or Zip Code::	
Country::	Italy

Correspondence Information

Correspondence Customer Number:: 23913

Representative Information

Representative Customer Number:: 23913

Assignee Information

Assignee Name:: Pfizer Inc.

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (c).

Express Mail Label No.

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Juan	Colberg	Norwich, CT
Maurizio	Zenoni	Milan, Italy
Giovanni	Fogliato	Bergamo, Italy
Alessandro	Donadelli	Lodi, Italy

☐ *Additional inventors are being named on the separately numbered sheets attached hereto.*

TITLE OF THE INVENTION *(280 characters max)*

COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS

CORRESPONDENCE ADDRESS

Direct all correspondence to:

☒ Customer Number 23913 →

☐ Firm or Individual Name					
Address					
Address					
City		State		ZIP	
Country		Telephone		Fax	

ENCLOSED APPLICATION PARTS *(check all that apply)*

☐ Specification — Number of Pages — ☐ CDs, Number

☐ Drawing(s) — Number of Sheets — ☐ Other (specify)

☒ Application Data Sheet. See 37 CFR1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

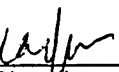
		FILING FEE AMOUNT($)
☐	Applicant claims small entity status. See 37 CFR1.27	
☐	A check or money order is enclosed to cover the filing fees	$50.00
☒	The Commissioner is hereby authorized to charge all required filing fees to, and credit any overpayment to Deposit Account Number: 16-1445	
☐	Payment by credit card Form PTO-2038 is attached.	

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE  DATE: March 8'02

TYPED or PRINTED NAME Elsa Djuanti REGISTRATION NO *(if appropriate)* 45,963

TELEPHONE 212 733 1417 Docket Number. PC10862

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
60/251,014	12/04/2000	Juan C. Colberg	PC10862

CONFIRMATION NO. 5041

FORMALITIES LETTER

OC000000007366637

Paul H Ginsburg
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755

Date Mailed: 01/25/2002

NOTICE TO FILE MISSING PARTS OF PROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(c)

Filing Date Granted

An application number and filing date have been accorded to this provisional application. The items indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(l) of $50 for a non-small entity, must be submitted with the missing items identified in this letter.
- The provisional application cover sheet under 37 CFR 1.51(c)(1), which may be an application data sheet (37 CFR 1.76), is required identifying:
  - either city and state or city or foreign country of the residence of each inventor.
- **The balance due by applicant is $ 50.**

A copy of this notice MUST be returned with the reply.

Customer Service Center
Initial Patent Examination Division (703) 308-1202

PART 3 - OFFICE COPY

Pfizer MAILING REQUEST *PLEASE PRINT*

ORIGINATED BY:	DATE	
Dr. E. Djuardi	3-8-02	
BUILDING/FLOOR/STOP NO.	DEPT. CHG. NO.	EXT.
150-05-49	88421	31417

SHIP TO: *(Street Address and Phone # Required on Label))*

COMMISSIONER FOR PATENTS
BOX MISSING PARTS
WASHINGTON, D.C. 20231

ZIP CODE 2 0 2 3 1

FIRST CLASS

SHIP-TO-NUMBER: ( )
(Phone contact required for all two-day or next-day deliveries.)

QUANTITY	COMPLETE DESCRIPTION
1	Env. - Legal documents. RE: PC10862 / EDJ

☐ No Value ☐ Insure For $ _____

Other (Please explain here)

International - Routing

☐ International Courier* ☐ Registered ☐ Air Mail
☐ Other - Explain *Customs forms will be provided by Shipping Dept. based on your complete description

Domestic Only - Routing

☒ First Class ☐ Insured ☐ Messenger
☐ Parcel Post (Third Class) ☐ Registered ☐ Truck
☐ Book Rate (Fourth Class) ☐ Certified ☐ UPS

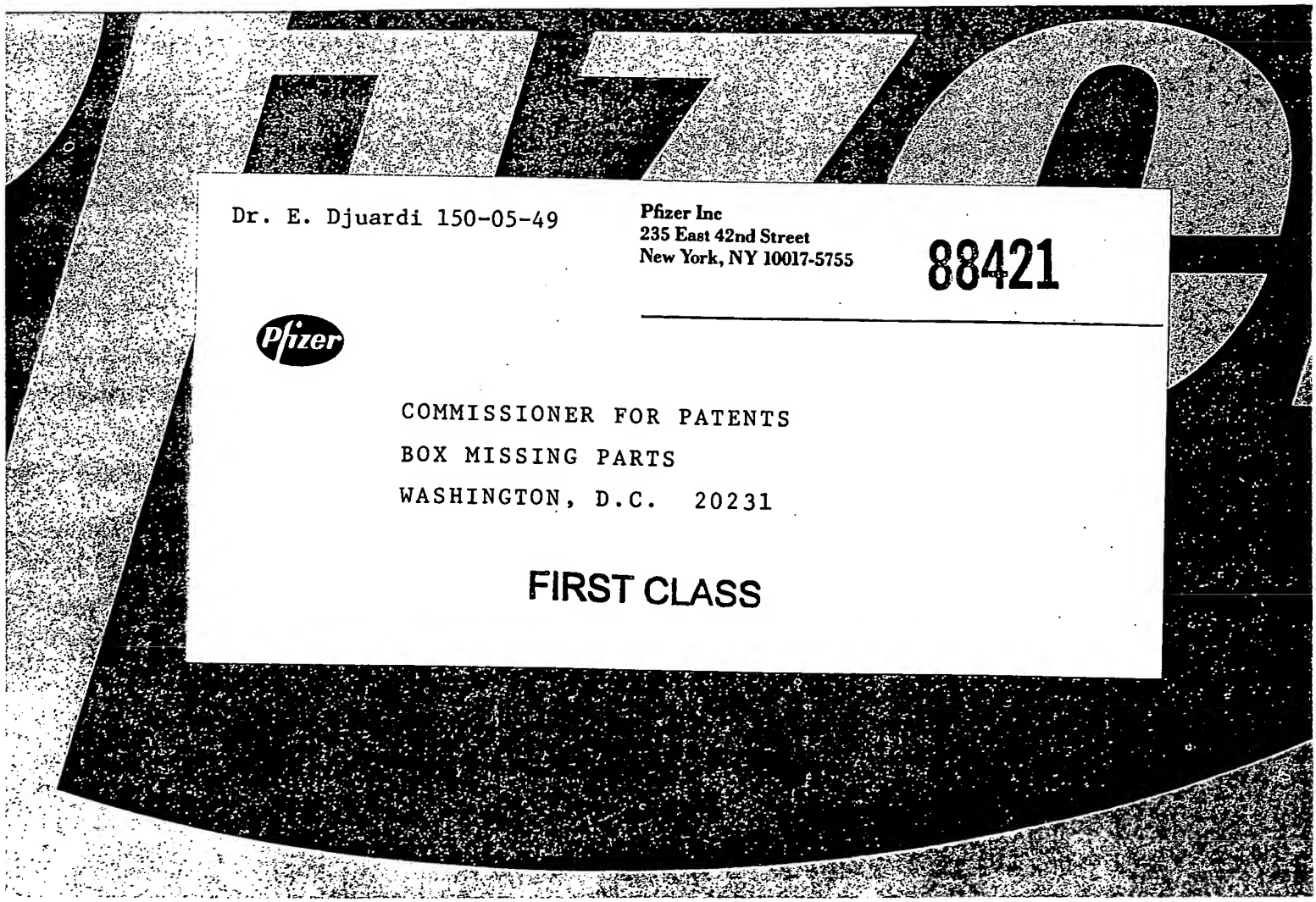
Domestic Only - Priority Options

☐ Next Business Day ☐ AM ☐ PM
☐ **Saturday Delivery Required**
Not all areas are serviced. Call Ext. 7796 to confirm your destination.
☐ USPS Express Mail Next Day (For Post Office Boxes Only)
☐ Second Business Day
☐ U.S. Postal Service Priority Mail

SPECIAL SERVICES

☐ No Signature Required (Federal Express, Express Mail)
☐ Bill Recipient/Third Party; Account # _____
☐ Return Receipt (Certified, Registered, Express Mail, Priority Mail, Messenger)
☐ Proof of Delivery (Fed Ex, DHL, U.P.S.)
☐ Pick-up Only (Messenger or Truck)
☐ Delivery & Pick-up (Messenger or Truck)
☐ Hold at Messenger Center for Pre-Arranged Messenger/Courier Pickup
☐ Other Explain _____

8385-1 (12/95) 3B PF-MSO-01



CHRON FILES

Express Mail No. EL639814149US Docket No. PC10862 By EXD

Serial No. ~~NOT YET ASSIGNED~~ Filing Date CONCURRENTLY HEREWITH

Application of Juan C. Colberg

Entitled Coupling Process and Intermediates Useful for Preparing Cephalosporins

The following, due _____ in the U.S. Patent Office, has been received there on the date stamped hereon:

- [X] Specification 26 pages
- [X] Claims 5 pages
- [X] Abstract 1 pages
- [ ] Drawing(s) ____ sheets
- [ ] Declaration with [ ] Power of Attorney
- [ ] Assignment & Recordation Cover Sheet
- [ ] Letter of Transmittal
- [XX] USPS Certificate of Mailing (Express Mail)
- [ ] Disclosure Statement ____ References
- [ ] Issue Fee Transmittal
- [ ] Fee Address Indication Form
- [ ] Affidavit [ ] Declaration [ ] Oath
- [ ] Certification 37 CFR 3.73(b)
- [ ] Notice of Appeal
- [ ] Amendment
- [ ] Brief (3 copies)
- [ ] Letter
- [ ] Petition for Extension of Time
- [ ] PTO-1390 (DO/EO/US) ____ pages
- [ ] Priority Document
- [XX] Provisional App. Cover Sheet
- [XX] _____
- [ ] _____
- [ ] _____

Patent Application
Attorney Docket No.PC10862

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: PC10862	:	Examiner: NOT YET ASSIGNED
APPLICATION NO.: NOT YET ASSIGNED	:	
FILING DATE: CONCURRENTLY HEREWITH	:	Group/Art Unit: NOT YET ASSIGNED
TITLE: COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS	:	

BOX PROVISIONAL PATENT APPLICATION
ASSISTANT COMMISSIONER OF PATENTS
WASHINGTON, D.C. 20231

Sir:

CERTIFICATE OF MAILING EXPRESS MAIL

EL639814149US

I hereby certify that this correspondence is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this 4 day of December, 2000.

By _____

Signature of person mailing
Elsa Djuardi (Reg. No. 45,963)

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (c).

	Docket Number	PC10862	Type a plus sign (+) inside this box	+

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
COLBERG	JUAN	C.	26 ROYAL OAKS DRIVE, NORWICH, CT 06360

TITLE OF THE INVENTION *(280 characters max)*

COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS

CORRESPONDENCE ADDRESS

Paul H. Ginsburg
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification Number of Pages **26** ☒ Claim(s) Number of Pages **5 pages**

☐ Drawing(s) Number of Sheets ☐ Other (specify) Abstract **1** page

METHOD OF PAYMENT *(check one)*

☐	A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT($)	**$150.00**
☒	The Commissioner is hereby authorized to charge all required filing fees to, and credit any overpayment to Deposit Account Number: 16-1445. Two copies of this page are enclosed.		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE  DATE: December 4, 2000

TYPED or PRINTED NAME Elsa Djuardi REGISTRATION NO: 45,963 *(if appropriate)*

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

CERTIFICATE OF MAILING - EXPRESS MAIL

PFIZER DOCKET NO: PC10862A

APPLICATION NUMBER: N/A

TITLE: : **COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS**

APPLICANT: Juan C. COLBERG et al

"Express Mail" mailing label number EL 874867545 US

Date of Deposit December 4, 2001

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Box Patent Application, Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Michelle Dungee

(Typed or printed name of person mailing paper or fee)

Michelle Dungee

(Signature of person mailing paper or fee)

Pfizer, Inc
Patent Department, 20th Floor
235 East 42nd Street
New York, NY 10017-5755

Application Information

Application Type::	Regular
Subject Matter::	Utility
Title::	COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS
Attorney Docket Number::	**PC10862A**

Inventor Information

Inventor Authority Type::	INVENTOR
Primary Citizenship Country::	US
Given Name::	Juan C.
Family Name::	Colberg
City of Residence::	Norwich
State or Prov of Residence::	CT
Country of Residence::	USA
Street::	26 Royal Oaks Drive
City::	Norwich
State or Province::	CT
Postal or Zip Code::	06360

Inventor Authority Type::	INVENTOR
Primary CitizenshipCountry::	Italy
Given Name::	Maurizio
Family Name::	Zenoni
City of Residence::	Milan
State or Prov of Residence::	
Country of Residence::	Italy
Street::	via Fleming 7
City::	Milan
State or Province::	Paullo
Postal or Zip Code::	20067
Country::	Italy

Inventor Authority Type::	INVENTOR
Primary Citizenship Country::	Italy
Given Name::	Giovanni
Family Name::	Fogliato
City of Residence::	Bergamo
State or Prov of Residence::	
Country of Residence::	Italy
Street::	via Mazzini 22
City::	Bergamo
State or Province::	Barzana
Postal or Zip Code::	24030

Inventor Authority Type::	INVENTOR
Primary Citizenship Country::	Italy
Given Name::	Alessandro
Family Name::	Donadelli
City of Residence::	Lodi
State or Prov of Residence::	
Country of Residence::	Italy
Street::	via Gramsci 42
City::	Lodi
State or Province::	Casalousterlengo
Postal or Zip Code::	26841

Correspondence Information

Correspondence Customer Number:: 23913

Representative Information

Representative Customer Number:: 23913

Assignee Information

Assignee Name:: Pfizer Inc.

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This application	Non Prov of Prov	60/251014	12/4/00

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FROM: (PLEASE PRINT) PHONE ( )

PFIZER INC
235 E 42ND ST
NEW YORK NY 10017-5703
Elsa Djuardi, Esq. (212) 733-1417
~~PC10862A~~ ~~PC10862A~~
PC10862A

TO: (PLEASE PRINT) PHONE ( )

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United States Patent & Trademark Office
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Keyword/Search

PC10862A EXD

Pfizer MAILING REQUEST *PLEASE PRINT*

ORIGINATED BY: ELSA DJUARDI | DATE 12/03/01

BUILDING/FLOOR/STOP NO. 150-03-49 | DEPT. OHC NO. 88421 | EXT. 3-3189

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QUANTITY	COMPLETE DESCRIPTION
	Patent application

☐ No Value ☐ Insure For $ _____

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☐ Other Explain _____

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PF-MSO-01

12/3/2001

39263

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Date Mailed: 12/3/01 Express Mail No. EL874867545 US

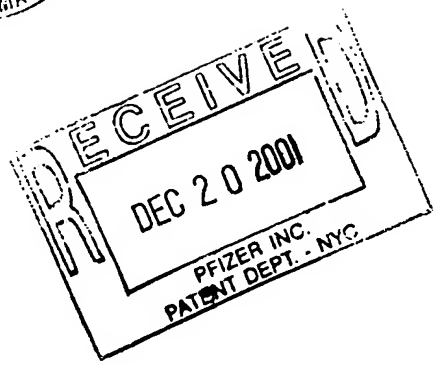
Serial No. Unassigned Docket No. PC10862A By EDJ:mdd

Application of Juan C. COLBERG et al. Filing Date Concurrent herewith

Entitled **COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS**

The following, has been received in the United States Patent and Trademark Office on the date stamped hereon:

- ☒ **Application Transmittal** *Type:* **Utility**
- ☒ **Specification 32** *pages*
- ☒ **Claims 5** *pages*
- ☒ **Abstract 1** *pages*
- ☐ Drawing(s) *sheets*
- ☐ Declaration with Power of Attorney
- ☐ Priority Document
- ☐ Disclosure Statement
- ☐ Form PTO-FB-A820 (Citation List) References
- ☐ Sequence Submission (☐Computer Readable Copy, ☐ Paper copy ☐ Identity Statement)
- ☐ Copy of Notice to File Missing Parts, Cover Letter
- ☒ **Amendment (Preliminary)**
- ☐ Reply
- ☐ Notice of Appeal
- ☐ Brief (3 copies)
- ☐ Issue Fee Transmittal
- ☐ Fee Address Indication Form
- ☐ Certificate of Correction
- ☐ Petition for Extension of Time
- ☐ Fee Transmittal (2 copies)
- ☐ Associate Power of Attorney
- ☐ Petition for Expedited Issuance for Foreign Filing License
- ☐ Assignment & Recordation Cover Sheet
- ☒ **Application Data Sheet**
- ☐
- ☐



Date Mailed: 12/3/01 **Express Mail No.** EL874867545 US

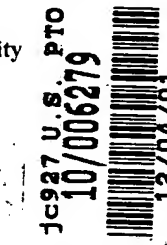
Serial No. Unassigned **Docket No.** PC10862A **By** EDJ:mdd

Application of Juan C. COLBERG et al. **Filing Date** Concurrent herewith

Entitled COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS

EDJ

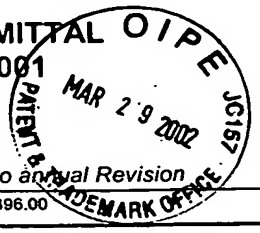
The following, has been received in the United States Patent and Trademark Office on the date stamped hereon:



- ☒ **Application Transmittal** *Type:* **Utility**
- ☒ **Specification 32** *pages*
- ☒ **Claims 5** *pages*
- ☒ **Abstract 1** *pages*
- ☐ Drawing(s) *sheets*
- ☐ Declaration with Power of Attorney
- ☐ Priority Document
- ☐ Disclosure Statement
- ☐ Form PTO-FB-A820 (Citation List) References
- ☐ Sequence Submission (☐Computer Readable Copy, ☐ Paper copy ☐ Identity Statement)
- ☐ Copy of Notice to File Missing Parts, Cover Letter
- ☒ **Amendment (Preliminary)**
- ☐ Reply
- ☐ Notice of Appeal
- ☐ Brief (3 copies)
- ☐ Issue Fee Transmittal
- ☐ Fee Address Indication Form
- ☐ Certificate of Correction
- ☐ Petition for Extension of Time
- ☐ Fee Transmittal (2 copies)
- ☐ Associate Power of Attorney
- ☐ Petition for Expedited Issuance for Foreign Filing License
- ☐ Assignment & Recordation Cover Sheet
- ☒ **Application Data Sheet**
- ☐
- ☐

PTO/SB/17(11-00)
Approved for use through 10/31//2002. OMB 0651-0032
U.S. P[illegible]nd Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork reduction Act of 1995, no persons are required to respond to a col[illegible] of information unles it displays a valid OMB control number.

FEE TRANSMITTAL For FY 2001



Patent Fees are subject to annual Revision

Total Amount of Payment	($)896.00

Complete if Known	
Application Number	Unassigned
Filing Date	Concurrent herewith
First Named Inventor	Juan C. Colberg
Examiner Name	Unassigned
Group/Art Unit	Unassigned
Attorney Docket No.	PC 10862A

METHOD OF PAYMENT

1. ☒ The commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 16-1445

Deposit Account Name: Pfizer Inc

☒ Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17

☐ Applicant claims small entity status. See 37 CFR 1.27

2. ☐ **Payment Enclosed:**

☐ Check ☐ Credit card ☐ Money Order ☐ Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	355	Utility filing fee	740
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	filing fee	
				SUBTOTAL (1) ($)	740

2. EXTRA CLAIM FEES

	Extra Claims		Fee from below		Fee Paid
Total Claims	24 -20**=	4	X 18	=	72
Independent Claims	4 - 3**=	1	X 84	=	84
Multiple Dependent				=	0

Large Entity Fee Code	Large Entity Fee Code	Small Entity Fee code	Small Entity Fee code	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	80	209	42	**Reissue independent claims over original patent
110	18	210	9	**Reissue claims in excess of 20 and over original patent
				SUBTOTAL (2) ($) 156

** or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Fee Code	Large Entity Fee ($)	Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge – late fee or oath	
127	50	227	25	Surcharge–late filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for *ex parte* reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55		
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55		
141	1,280	241	640	Petition to revive – unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Processing fee under 37 CFR 1.17(q)	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR § 1.129(b))	
179	710	279	355	Request for Continued Examination(RCE)	
169	900	169	900	Request for expedited examination of a design application	
Other (specify)					0
*Reduced by Basic Filing Fee Paid				Subtotal (3)	

SUBMITTED BY

Complete (if applicable)

Type or Printed Name	Elsa Djuardi	Registration No. (Attorney/Agent)	45,963	Telephone	
Signature				Date	December 4, 2001

PTO/SB/05 (3-01)
Approved for use through 09/30/2000. OMB 0651-0032
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Please type a plus sign (+) inside this box →

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonapplications under 37C.F.R. §1.53(b))

Attorney Docket No.	PC 10862A
First Inventor	Juan C. Colberg
Title	COUPLING PROCESS AND INTERMEDIATES USEFUL FOR
Express Mail Label No.	EL 874867545 US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Commissioner for Patents, Box Patent Application, Washington, DC 20231

1. ☒ *Fee Transmittal Form (e.g., *PTO/SB/17*) *(Submit an original, and a duplicate for fee processing)*
2. ☐ Applicant claims small entity status See 37 CFR 1.27
3. ☒ Specification [Total Pages 38]
   (preferred arrangement set forth below)
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R&D
   - Reference to sequence listing, a table, or a computer program listing appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
4. ☐ Drawing(s) *(35 U.S.C. 113)* [Total sheets]
5. ☐ Oath or Declaration [Total pages]
   a. ☐ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 CFR §1.63(d)) *(for continuation/divisional with Box 18 completed)*
      i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. ☒ Application Data Sheet. See 37 CFR 1.76
7. ☐ CD-ROM or CD-R in duplicate, large table or computer Program (Appendix)
8. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. ☐ Computer Readable Copy (CRF)
   b. Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies)
      ii. ☐ Paper
   c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. ☐ Assignment Papers (cover sheet & document(s))
10. ☐ 37 CFR 3.73(b) Statement ☐ Power of Attorney *(when there is an assignee)*
11. ☐ English Translation Document *(if applicable)*
12. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
13. ☒ Preliminary Amendment
14. ☒ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. ☐ Nonpublication Request under 35 U.S.C. 122 (b)(2)(B)(i). Applicant must attach form PTO/SB/35 or its equivalent.
17. ☐ Other:

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in a preliminary amendment, or in an Application Data Sheet under 37CFR 1.76.*

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No: ____/____

Prior application information: *Examiner* _____ *Group/Art Unit:* _____

For CONTINUATION OR DIVISIONAL APPS only. The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts

18. CORRESPONDENCE ADDRESS

☒ *Customer Number or Bar Code Label* *(Insert Customer No. or Attach bar code label here)* 23913 *or* ☐ *Correspondence address below*

Name					
Address					
City		State		Zip Code	
Country		Telephone		Fax	

NAME (Print/type)	Elsa Djuardi	*Registration No. (Attorney/Agent)*	45,963
Signature		*Date*	12/4/01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION OF: Juan C. Colberg *et al.*
APPLICATION NO.: Unassigned Examiner: To Be Assigned
FILING DATE: Concurrent Herewith
TITLE: COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS

Box Patent Application
Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

Kindly amend this application as follows:

IN THE SPECIFICATION

Page 1, after the title, add:

--This application claims priority under 35 U.S.C. §119(e) of U.S. application serial no. 60/251014 filed December 4, 2000, which application is hereby incorporated by reference herein.--

Respectfully submitted,

Date: December 4'01

Elsa Djuardi
Reg. No. 45,963
Attorney for Applicants

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
60/251,014	12/04/2000		0.00	PC10862			

CONFIRMATION NO. 5041

FILING RECEIPT

OC000000007366636

Paul H Ginsburg
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755

Date Mailed: 01/25/2002

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Juan C. Colberg, Norwich, CT;
Maurizio Zenoni, Residence Not Provided;
Alessandro Donadelli, Residence Not Provided;
Giovanni Fogliato, Residence Not Provided;

If Required, Foreign Filing License Granted 01/25/2002

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

Coupling process and intermediates useful for preparing cephalosporins

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LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
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APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
60/251,014	12/04/2000	Juan C. Colberg	PC10862

CONFIRMATION NO. 5041

FORMALITIES LETTER

OC000000007366637

Paul H Ginsburg
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755

Date Mailed: 01/25/2002

NOTICE TO FILE MISSING PARTS OF PROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(c)

EIS

Filing Date Granted

An application number and filing date have been accorded to this provisional application. The items indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(l) of $50 for a non-small entity, must be submitted with the missing items identified in this letter.
- The provisional application cover sheet under 37 CFR 1.51(c)(1), which may be an application data sheet (37 CFR 1.76), is required identifying:
  - either city and state or city or foreign country of the residence of each inventor.
- **The balance due by applicant is $ 50.**

A copy of this notice MUST be returned with the reply.

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 1 - ATTORNEY/APPLICANT COPY

COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS

Background of the Invention

This invention relates to a novel process for the preparation of 3-cyclic-ether-substituted cephalosporins. The invention also relates to novel processes for preparing zwitterions, para-nitrobenzyl esters and allyl esters useful in the preparation of the above cephalosporins. The invention also relates to 3-cyclic-ether-substituted cephalosporins. These compounds possess certain advantageous properties, such as crystalline form and high enantiomeric excess (e.e.).

The 3-cyclic-ether-substituted cephalosporins prepared by the methods of the present invention have prolonged and high levels of antibacterial activity and possess good absorption parentally in humans and animals. The 3-cyclic-ether-substituted cephalosporins prepared by the processes of the present invention contain a cyclic ether substituent at carbon 3 of the cephalosporin nucleus.

GB 1405758 describes alternative methods of preparation of certain 3-cyclic-ether-substituted cephalosporins.

J. Antibiotics (1994), vol. 47(2), page 253, and WO 92/01696 also describe alternative methods of preparation of compounds of formula I, as defined herein below, and compounds useful in said processes.

United States Patents No. 6,020,329 and 6,077,952 describe salts, polymorphs, solvates and hydrates of 3-cyclic-ether-substituted cephalosporins.

United States Patent No. 6,001,997 describes alternative methods of preparations of 3-cyclic-ether-substituted cephalosporins.

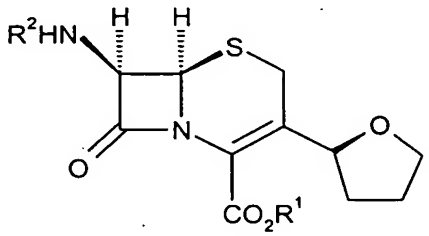
United States Non-Provisional Patent Application entitled "Process and Ester Derivatives Useful For Preparation of Cephalosporins", filed December 4, 2001, refers to intermediates and processes to prepare 3-cyclic-ether-substituted cephalosporins.

Each of the above referenced publications, patents and patent applications is hereby incorporated by reference in its entirety.

The present inventors have discovered a novel compound of formula I, as defined herein below. The present inventors have also discovered a high-yielding process for the preparation of said compounds of formula I.

Summary of the Invention

The present invention relates to a process for the preparation of a 3-cyclic-ether-substituted cephalosporin of the formula I



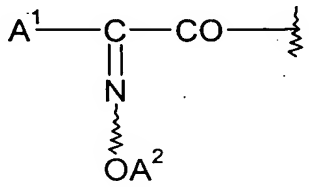
I

or the pharmaceutically acceptable salts thereof,

wherein

the group CO_2R^1 is a carboxylic acid or a carboxylate salt; and

R^2 has a formula:



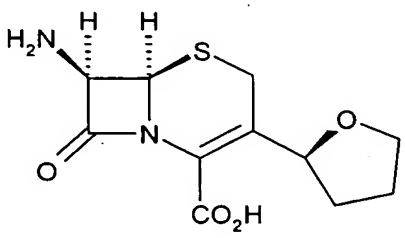
wherein

A^1 is C_{6-10}aryl, C_{1-10}heteroaryl or C_{1-10}heterocyclyl;

A^2 is hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-10}aryl, C_{1-6}alkyl(CO)(C_{1-6})alkyl-O-, HO(CO)(C_{1-6})alkyl, mono-(C_{6-10}aryl)(C_{1-6}alkyl), di-(C_{6-10}aryl)(C_{1-6}alkyl) or tri-(C_{6-10}aryl)(C_{1-6}alkyl);

comprising reacting

a compound of formula II



II

with a compound of the formula III

$$R^2L \qquad \text{(III)}$$

wherein R^2 is as defined above, and L is a leaving group, in the presence of a solvent and a base. Optionally, the aforesaid process may be performed in the presence of a coupling agent and a catalyst.

Preferably, the group OA^2 of said compounds of formula **III** is cis to the amide linkage, i.e., the Z-configuration is preferred.

Suitable solvents for the aforesaid process of conversion of compounds of formula **II** into compounds of formula **I** of the invention include water, acetone, tetrahydrofuran, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, methylene chloride, 1,2-dichloroethane or mixtures thereof. In one embodiment of the invention, the solvent is tetrahydrofuran. In another embodiment of the invention, the solvent is ethyl acetate. Preferably, the solvent is water, acetone or mixtures thereof. More preferably the solvent is a mixture of acetone and water. Most preferably the solvent is a 1.3:1 mixture of acetone and water.

Suitable bases for the aforesaid conversion of the invention include diisopropylethylamine or sodium hydroxide. Preferably, the base is sodium hydroxide, most preferably 15% aqueous sodium hydroxide.

Suitable coupling agents for the aforesaid conversion of the invention include N,N'-diethylcarbodiimide, N,N'-dipropyl carbodiimide, N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, N-ethyl-N'-[3-(dimethylamino)propyl]carbodiimide, N,N'-carbonyldiimidazole or N,N'-carbonyldithiazole. A preferred coupling agent is N,N'-dicyclohexylcarbodiimide. Preferably, the aforesaid conversion is conducted in the absence of any coupling agents.

Suitable catalysts for the aforesaid conversion of the invention include Lewis acids. Suitable Lewis acids are selected from the group consisting of boron trihalide, such as boron tribromide, and aluminum halide, such as aluminum chloride. Preferably, the aforesaid conversion is conducted in the absence of any catalysts.

The aforesaid conversion of the invention can be conducted at a temperature of about -40°C to about +30°C, preferably about +20°C to about +30°C. The aforesaid process can be conducted for a period from about 1 hour to about 24 hours; preferably about 3 hours.

Suitable leaving groups L of the aforesaid compound of formula **III** of the aforesaid conversion include hydroxy, halo, azido, mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate, mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di(C_{1-6}alkyl)phosphorothioate, (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, (C_{1-6}alkyl)-(CO)-S-, cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy or N-oxy-succinimidyl.

In one embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of hydroxy, halo and azido.

In another embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate, mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate and di(C_{1-6}alkyl)phosphorothioate.

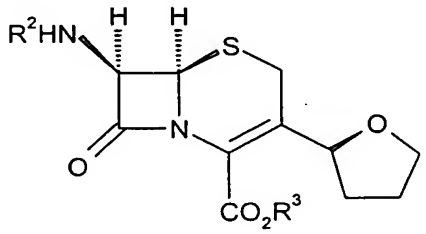
In yet another embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl and (C_{1-6}alkyl)-(CO)-S-.

In yet another embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy and N-oxy-succinimidyl.

In yet another embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of halo, methanesulfonyl, diethylphosphorothioate and 3-benzthiazolyloxy.

In a preferred embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is di(C_{1-6}alkyl)phosphorothioate, more preferably diethylphosphorothioate.

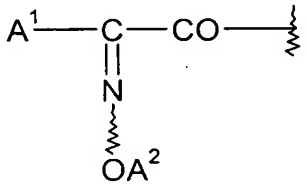
The present invention also relates to an alternative process for the preparation of the above 3-cyclic-ether-substituted cephalosporin of the formula **I**, or the pharmaceutically acceptable salts thereof, comprising reacting a compound of formula **V**



V

wherein

R^2 has the formula



wherein

A^1 is C_{6-10}aryl, C_{1-10}heteroaryl or C_{1-10}heterocyclyl;

A^2 is hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-10}aryl, C_{1-6}alkyl(CO)(C_{1-6})alkyl-O-, HO(CO)(C_{1-6})alkyl, mono-(C_{6-10}aryl)(C_{1-6}alkyl), di-(C_{6-10}aryl)(C_{1-6}alkyl) or tri-(C_{6-10}aryl)(C_{1-6}alkyl); and

R^3 is para-nitrobenzyl or allyl, preferably allyl;

with a suitable deprotecting agent in the presence of a solvent.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched moieties or combinations thereof. alkyl groups, wherever they occur, may be optionally substituted by a suitable substituent.

The term "cycloalkyl", as used herein, unless otherwise indicated, includes a mono or bicyclic carbocyclic ring (*e.g.,* cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl and bicyclo[5.2.0]nonanyl, etc.); optionally containing 1or 2 double bonds and optionally substituted by 1 to 3 suitable substituents as defined below such as fluoro, chloro, trifluoromethyl, (C_{1-4})alkoxy, (C_{6-10})aryloxy, trifluoromethoxy, difluoromethoxy or (C_{1-4})alkyl, more preferably fluoro, chloro, methyl, ethyl and methoxy.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is as defined above.

The term "halo", as used herein, unless otherwise indicated, includes fluorine, chlorine, bromine or iodine, preferably bromine or chlorine.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one or more hydrogen(s), such as phenyl or naphthyl, optionally substituted by 1 to 3 suitable substituents such as fluoro, chloro, cyano, nitro, trifluoromethyl, (C_{1-6})alkoxy, (C_{6-10})aryloxy, (C_{3-8})cycloalkyloxy, trifluoromethoxy, difluoromethoxy or (C_{1-6})alkyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one or more hydrogen(s), such as benzimidazolyl, benzofuranyl, benzofurazanyl, 2H-1-benzopyranyl, benzothiadiazine, benzothiazinyl, benzothiazolyl, benzothiophenyl, benzoxazolyl, chromanyl, cinnolinyl, furazanyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrazolyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiazolyl, thiadiazolyl, thienyl, triazinyl and triazolyl, wherein said (C_{1-10})heteroaryl is optionally substituted on any of the ring carbon atoms capable of forming an additional bond by one or two substituents independently selected from F, Cl, Br, CN, OH, (C_{1-4})alkyl, (C_{1-4})perfluoroalkyl, (C_{1-4})perfluoroalkoxy, (C_{1-4})alkoxy and (C_{3-8})cycloalkyloxy. The foregoing groups, as derived

from the compounds listed above, can be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole can be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached).

The term "heterocyclyl", as used herein, unless otherwise indicated, includes an organic radical derived from a non-aromatic heterocyclic compound by removal of one or more hydrogens, such as 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]-heptanyl, azetidinyl, dihydrofuranyl, dihydropyranyl, dihydrothienyl, dioxanyl, 1,3-dioxolanyl, 1,4-dithianyl, hexahydroazepinyl, hexahydropyrimidine, imidazolidinyl, imidazolinyl, isoxazolidinyl, morpholinyl, oxazolidinyl, piperazinyl, piperidinyl, 2H-pyranyl, 4H-pyranyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, quinolizinyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2,3,6-tetrahydropyridinyl, tetrahydrothienyl, tetrahydrothiopyranyl, thiomorpholinyl, thioxanyl and trithianyl. The foregoing groups, as derived from the compounds listed above, can be C-attached or N-attached where such is possible. For example, a group derived from piperidine can be piperidin-1-yl (N-attached) or piperidin-4-yl (C-attached). The foregoing groups, as derived from the compounds listed above, can be optionally substituted where such is possible by a suitable substituent, such as oxo, F, Cl, Br, CN, OH, (C_{1-4})alkyl, (C_{1-4})perfluoroalkyl, (C_{1-4})perfluoroalkoxy, (C_{1-4})alkoxy, or (C_{3-8})cycloalkyloxy.

The phrase "a suitable substituent" is intended to mean a chemically and pharmaceutically acceptable functional group *i.e.*, a moiety that does not negate the inhibitory activity of the inventive compounds. Such suitable substituents may be routinely selected by those skilled in the art. Illustrative examples of suitable substituents include, but are not limited to halo groups, perfluoroalkyl groups, perfluoroalkoxy groups, alkyl groups, hydroxy groups, oxo groups, mercapto groups, alkylthio groups, alkoxy groups, aryl or heteroaryl groups, aryloxy or heteroaryloxy groups, aralkyl or heteroaralkyl groups, aralkoxy or heteroaralkoxy groups, carboxy groups, amino groups, alkyl- and dialkylamino groups, carbamoyl groups, alkylcarbonyl groups, alkoxycarbonyl groups, alkylaminocarbonyl groups dialkylamino carbonyl groups, arylcarbonyl groups, aryloxycarbonyl groups, alkylsulfonyl groups, arylsulfonyl groups and the like.

The term "carboxylate salt", as used herein, includes metal salts (such as aluminium, alkali metal salts, such as sodium or potassium, preferably sodium), alkaline earth metal salts (such as calcium or magnesium), and ammonium salts. The ammonium salts can be substituted with C_{1-6}alkylamines (such as triethylamine), hydroxy-(C_{1-6})alkylamines (such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine, or tris-(2-hydroxyethyl)amine), cycloalkylamines (such as dicyclohexylamine), procaine, dibenzylamine, N,N-dibenzylethylenediamine, 1-ephenamine, N-methylmorpholine, N-ethylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bis-dehydro-abietylamine,

ethylenediamine, or pyridine-type bases (such as pyridine, collidine or quinoline), or other amines which have been used to form salts with known penicillins and 3-cyclic-ether-substituted cephalosporins. Other useful salts include the lithium salt and silver salt. Salts within compounds of formula I can be prepared by salt exchange in conventional manner.

The term "active compounds", as used herein, refers to compounds of formula **I**.

Compounds of formula **I** contain chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers, enantiomers, diastereomers and stereoisomers of the compounds of formula I and mixtures thereof. The compounds of the invention also exist in different tautomeric forms. This invention relates to all tautomers of formula **I**. Those skilled in the art are well aware that the cephalosporin nucleus exists as a mixture of tautomers in solution. The various ratios of the tautomers in solid and liquid form is dependent on the various substituents on the molecule as well as the particular crystallization technique used to isolate a compound.

Preferably, the group OA^2 of said compounds of formula **III** is cis to the amide linkage, i.e., the Z-configuration is preferred.

Suitable deprotecting agents for the aforesaid process of conversion of compounds of formula **V** into compounds of formula **I** of the invention include sodium dithionite or tetrakis triphenyl phosphine palladium (0).

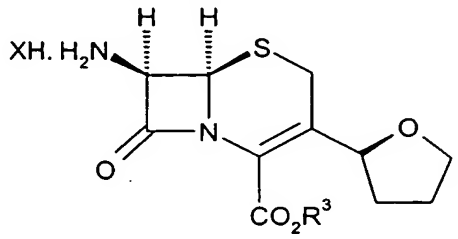
Suitable solvents for the aforesaid conversion include acetone, water, tetrahydrofuran, methylene chloride or mixtures thereof. In one embodiment of the invention, the solvent is methylene chloride, tetrahydrofuran or mixtures thereof. In another embodiment of the invention, the solvent is tetrahydrofuran. In a preferred embodiment of the aforesaid conversion of the invention, the solvent is methylene chloride.

The aforesaid conversion may be conducted at a temperature of about 0°C to about 45°C. The aforesaid conversion may be conducted for a period from about 1 hour to about 24 hours.

In one embodiment of the aforesaid conversion, R^3 is para-nitrobenzyl. Within, this embodiment, suitably the deprotecting agent is sodium dithionite. Within this embodiment, suitably the aforesaid conversion is conducted at a temperature of about 40°C. Within this embodiment, suitably the aforesaid process is conducted for about 4 hours.

In a preferred embodiment of the aforesaid conversion, R^3 is allyl. Within this embodiment, the preferred deprotecting agent is tetrakis triphenyl phosphine palladium (0). Within this embodiment, the aforesaid process is conducted at a temperature of about 20°C to about 35°C; preferably about 27°C to about 30°C. Within this embodiment, preferably the aforesaid process is conducted for about 5 hours.

The present invention also includes a process for the preparation of the above compound of formula **II** comprising reacting a compound of formula **IV**



IV

wherein R^3 is para-nitrobenzyl or allyl, preferably para-nitrobenzyl; and X is halo, preferably chloro; with a suitable deprotecting agent; in the presence of a solvent.

Suitable solvents for the process of conversion of compounds of formula **IV** into compounds of formula **II** of the invention include acetone, water, tetrahydrofuran, methylene chloride or mixtures thereof. In one embodiment of the invention, the solvent is acetone, water, tetrahydrofuran or mixtures thereof. Preferably, the solvent is a mixture of acetone and water. More preferably, the solvent is a 3:1 mixture of acetone and water.

Suitable deprotecting agents for the aforesaid conversion include sodium dithionite, catalytic hydrogenating agent (such as hydrogen gas over 10% palladium over carbon) or tetrakis triphenyl phosphine palladium (0).

The aforesaid conversion may be conducted at a temperature of about 0°C to about 45°C. The aforesaid conversion may be conducted for a period from about 1 hour to about 24 hours.

In the preferred embodiment of the aforesaid conversion, R^3 is para-nitrobenzyl. Within this embodiment, the preferred deprotecting agent is sodium dithionite. Preferably, the aforesaid process is conducted at a temperature of about 45°C. Preferably, the aforesaid process is conducted at a temperature of about 1 hour.

In another embodiment of the invention, R^3 is allyl. Within this embodiment, suitably the deprotecting agent is tetrakis triphenyl phosphine palladium (0). Suitable solvents include methylene chloride and tetrahydrofuran. The aforesaid process can be conducted at a temperature of about 20°C to about 35°C.

The present invention also relates to a process for the preparation of the above compound of formula **V** comprising reacting the above compound of formula **IV**, wherein R^3 is para-nitrobenzyl or allyl; preferably allyl; and X is halo; preferably chloro; with a compound of the formula **III**, as defined above, in the presence of a solvent. Optionally, the aforesaid process can be conducted in the presence of an optional coupling agent or an optional catalyst.

Suitable solvents for the aforesaid conversion of compounds of formula **IV** into compounds of formula **V** include methylene chloride, tetrahydrofuran or mixtures thereof.

In one embodiment of the aforesaid conversion of the invention, a coupling agent is used. Within this embodiment, suitable coupling agents include N,N'-diethylcarbodiimide, N,N'-dipropyl carbodiimide, N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, N-ethyl-N'-[3-(dimethylamino)propyl]carbodiimide, N,N'-carbonyldiimidazole or N,N'-carbonyldithiazole. A preferred coupling agent is N,N'-dicyclohexylcarbodiimide. Preferably, the aforesaid conversion is conducted in the absence of any coupling agents.

In another embodiment of the aforesaid conversion of the invention, a catalyst is used. Within this embodiment, the catalyst can be a Lewis acid. Suitable Lewis acids are boron trihalide, such as boron tribromide, or aluminum halide, such as aluminum chloride. Preferably, the aforesaid conversion is conducted in the absence of any catalysts.

The aforesaid conversion may be conducted at a temperature of about -40°C to about +40°C. The aforesaid conversion may be conducted for a period of from about 1 hour to about 24 hours.

In one embodiment of the aforesaid conversion of the invention, R^3 is para-nitrobenzyl. Within this embodiment, suitably the aforesaid conversion is conducted at a temperature of about +20°C to about +30°C. Within this embodiment, suitably the aforesaid conversion is conducted for about 3 hours.

In a preferred embodiment of the aforesaid conversion of the invention, R^3 is allyl. Within this embodiment, preferably the solvent is methylene chloride. Within this embodiment, preferably the aforesaid conversion is conducted at a temperature of about 20°C to about 40°C. Within this embodiment, preferably the aforesaid conversion is conducted for about 24 hours.

Suitably the leaving group L of the compound of formula **III** in the aforesaid conversion of the invention includes hydroxy, halo, azido, mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate, mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di(C_{1-6}alkyl)phosphorothioate, (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, (C_{1-6}alkyl)-(CO)-S-, cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy or N-oxy-succinimidyl.

In one embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of hydroxy, halo and azido.

In another embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate,

mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate and di(C_{1-6}alkyl)phosphorothioate.

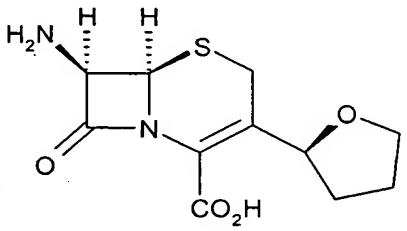
In yet another embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl and (C_{1-6}alkyl)-(CO)-S-.

In yet another embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy and N-oxy-succinimidyl.

In yet another embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is selected from the group consisting of halo, methanesulfonyl, diethylphosphorothioate and 3-benzthiazolyloxy.

In a preferred embodiment of the aforesaid conversion of the invention, the leaving group L of the compound of formula **III** is mono(C_{1-6}alkyl)carbonate, more preferably acetate.

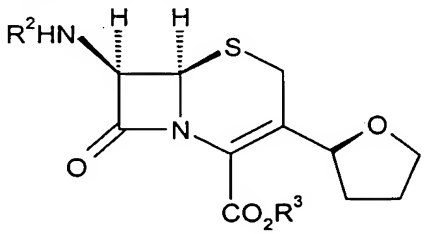
The present invention also relates to a compound of formula **II**



II

In one embodiment of the invention, the compound of formula **II** has an enantiomeric or diastereomeric purity of 96% to 100%; preferably 97%.

The present invention also relates to a compound of formula **V**



V;

wherein R^2 is as defined above; and R^3 is para-nitrobenzyl or allyl; preferably allyl.

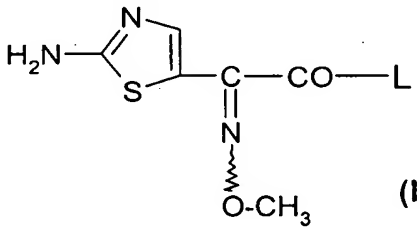
In one embodiment of the invention, the compound of formula **V** has an enantiomeric or diastereomeric purity of 96% to 100%; preferably 97%.

In generic or sub-generic embodiments of each of the foregoing embodiments, the A^1 moiety of said R^2 is C_{6-10}aryl, such as phenyl. In other generic or sub-generic embodiments of the invention, the A^1 moiety of said R^2 is C_{1-10}heteroaryl selected from the group consisting of

furyl, thienyl, pyridyl, aminothiazolyl and aminothiadiazolyl, in which the amino moiety of said aminothiazolyl or aminothiadiazolyl is optionally protected. In other generic or sub-generic embodiments of the invention, the A^1 moiety of said R^2 is C_{1-10}heterocyclyl; such as 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]-heptanyl, azetidinyl, dihydrofuranyl, dihydropyranyl, dihydrothienyl, dioxanyl, 1,3-dioxolanyl, 1,4-dithianyl, hexahydroazepinyl, hexahydropyrimidine, imidazolidinyl, imidazolinyl, isoxazolidinyl, morpholinyl, oxazolidinyl, piperazinyl, piperidinyl, 2H-pyranyl, 4H-pyranyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, 2-pyrrolinyl, 3-pyrrolinyl, quinolizinyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2,3,6-tetrahydropyridinyl, tetrahydrothienyl, tetrahydrothiopyranyl, thiomorpholinyl, thioxanyl or trithianyl. Preferably the A^1 moiety of said R^2 is aminothiazolyl.

In other generic or sub-generic embodiments of the invention, the A^2 moiety of said R^2 is hydrogen or C_{1-6}alkyl. A preferred embodiment of the invention includes each of the foregoing generic and sub-generic embodiments wherein the A^2 moiety of said R^2 is C_{1-6}alkyl, more preferably methyl.

In a preferred embodiment of each of the foregoing generic and sub-generic embodiments the invention, a compound of the formula **III** has a formula **IIIa**



(IIIa)

wherein L is a leaving group, such as halo, methanesulfonyl, dialkylphosphorothioate, such as diethylphosphorothioate or 3-benzthiazolyloxy.

In a most preferred embodiment of each of the foregoing embodiments of the invention, a compound of the formula **III** has a formula **IIIa**, as defined above, wherein L is diethylphosphorothioate or acetate.

The optional conversion of R^2 to a different R^2 and the optional formation of a pharmaceutically acceptable salt, can be carried out using methods well known in the art.

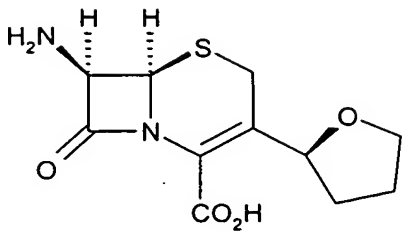
In the processes described hereinabove and hereinbelow, it may be necessary to remove protecting groups. Deprotection can be carried out by any convenient method known in the art such that unwanted side reactions are minimized. Separation of unwanted by-products can be carried out using standard methods known to those skilled in the art (for example, see "Protection of the Amino Group", in *Protective Groups in Organic Synthesis*, 2nd Edition, T. W. Greene and P.G. M. Wuts, Ed., Wiley and Sons, Inc. 1991, pp. 309-405).

The present invention also relates to a method of using a zwitterion intermediate for the preparation of 3-cyclic-ether-substituted cephalosporins.

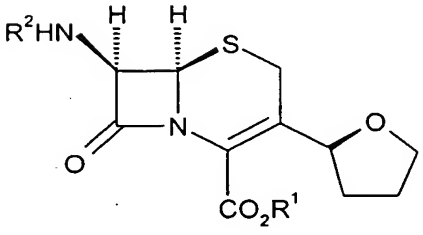
Detailed Description of the Invention

The process of the present invention and the preparation of the compound of the present invention are illustrated in the following reaction schemes. Except where otherwise indicated, in the reaction schemes and discussion that follow, substituents R^1, R^2, R^3, L, A^1, A^2 and X are as defined above unless otherwise described.

SCHEME 1

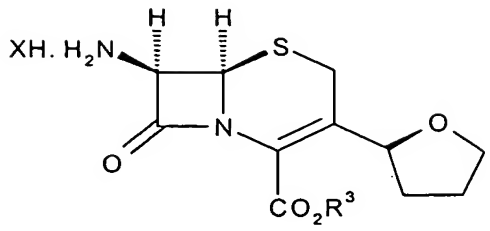


II

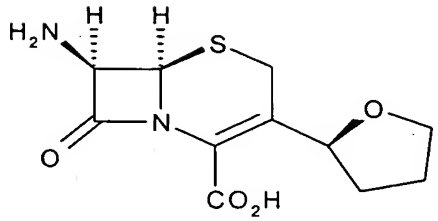


I

SCHEME 2

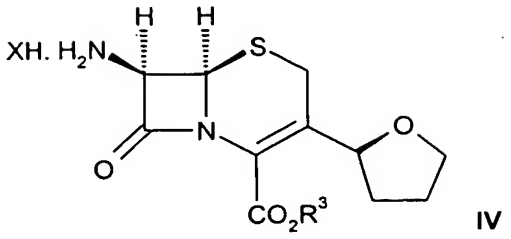


IV

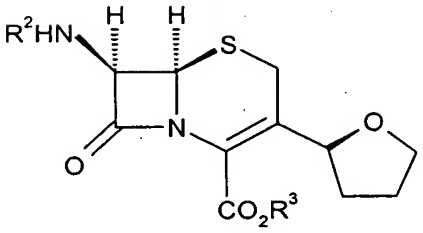


II

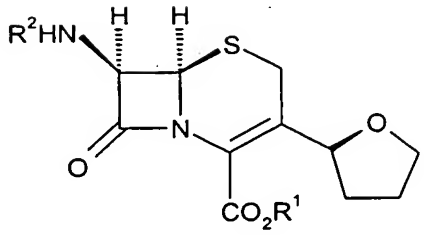
SCHEME 3



IV

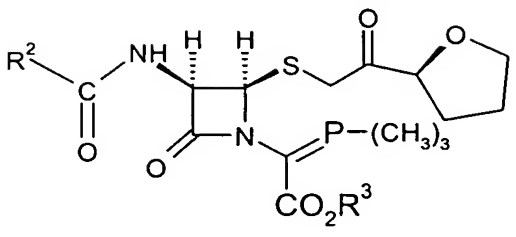


V

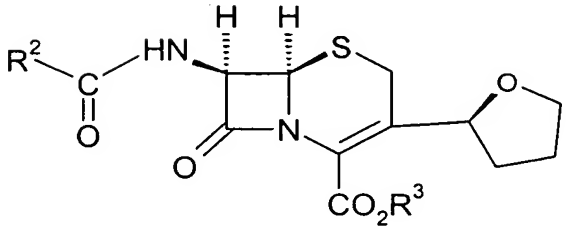


I

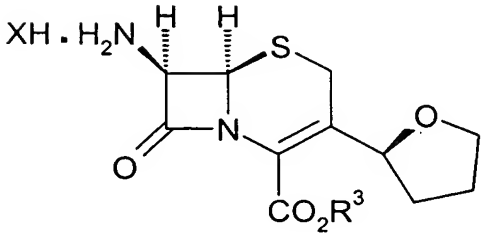
SCHEME 4



VIIa

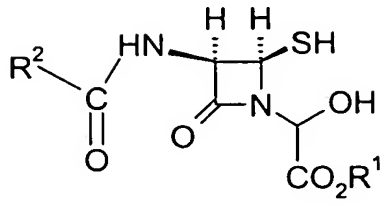


VI

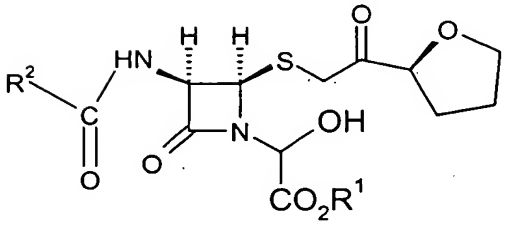


IV

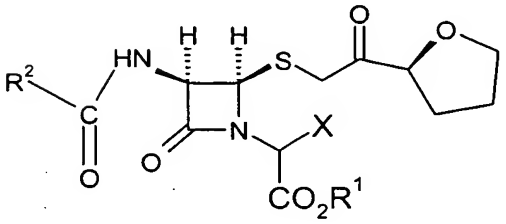
SCHEME 5



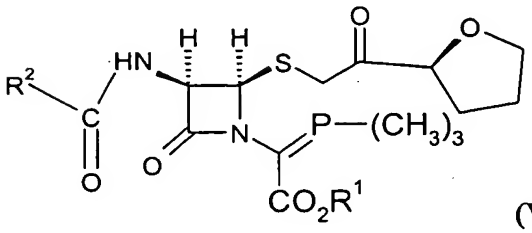
(VIII)



(VII)c

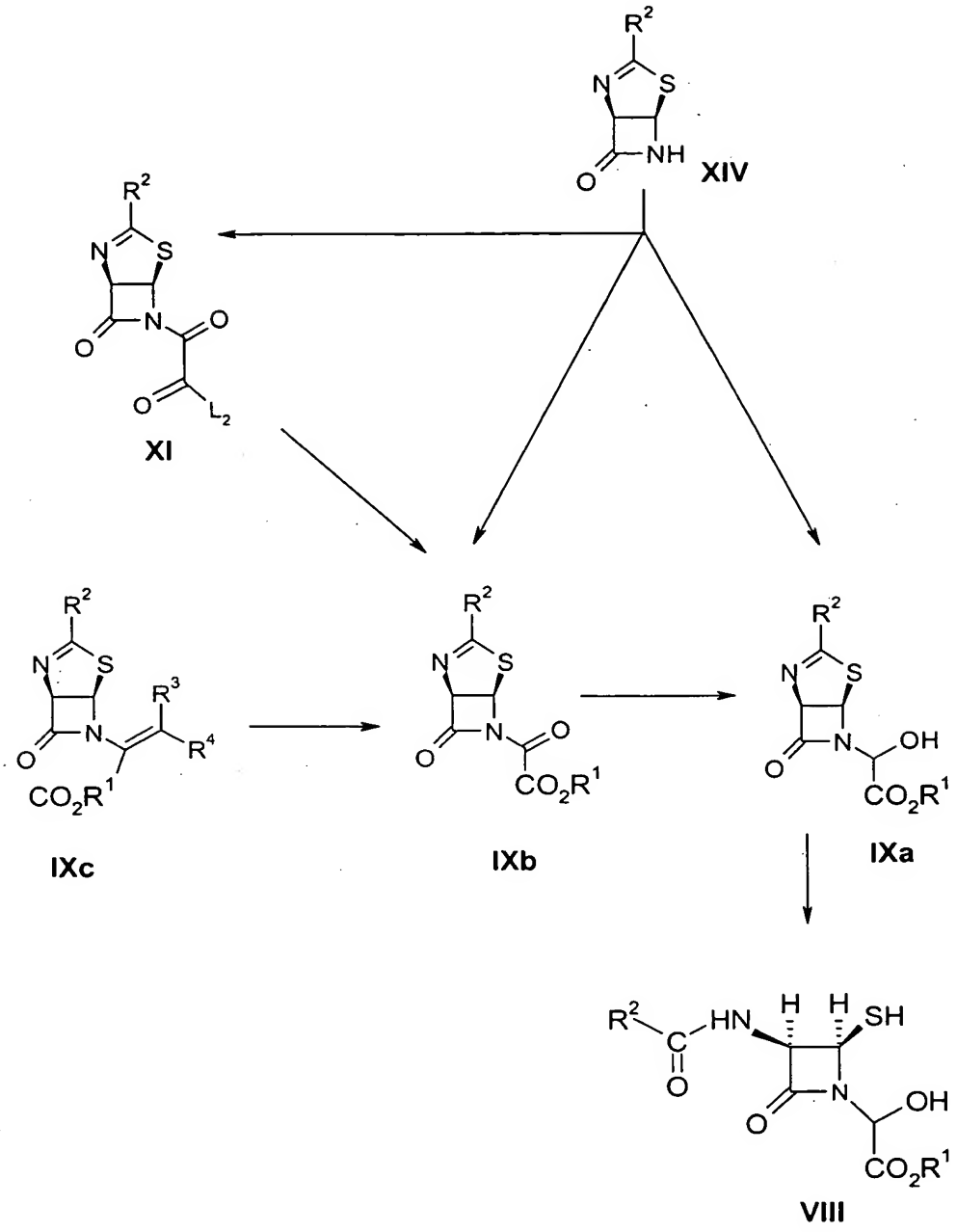


(VII)b



(VII)a

SCHEME 6


R2
N
S
NH
O
XIV
R2
N
S
N
O
O
O
O
L2
XI
R2
N
S
R3
N
O
R4
CO2R1
IXc
R2
N
S
N
O
O
CO2R1
IXb
R2
N
S
N
O
OH
CO2R1
IXa
R2
C
O
HN
H
H
SH
N
O
OH
CO2R1
VIII

Scheme 1 refers to the preparation of compounds of formula **I**. Referring to Scheme 1, a compound of formula **I** can be prepared by reacting a compound of formula **II** with a compound of formula **III**

$$R^2\text{-}L \qquad \text{(III)};$$

wherein L is a leaving group, in the presence of a base and a solvent.

Suitable leaving groups include hydroxy, halo, azido, mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate, mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di(C_{1-6}alkyl)phosphorothioate, (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, (C_{1-6}alkyl)-(CO)-S-, cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy or N-oxy-succinimidyl. Preferably, the leaving group is di(C_{1-6}alkyl)phosphorothioate, such as diethylphosphorothioate.

Suitable bases include diisopropylethylamine or sodium hydroxide, preferably sodium hydroxide, most preferably 15% aqueous sodium hydroxide.

Suitable solvents include water, acetone, tetrahydrofuran, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, methylene chloride, 1,2-dichloroethane, or mixtures thereof; preferably a mixture of water and acetone, most preferably a mixture of 1:1.3 of water and acetone.

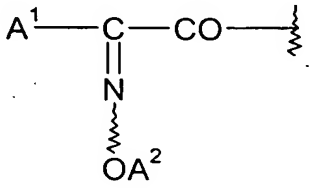
The aforesaid reaction can be conducted at a temperature of about -40°C to about 30°C; preferably about 20°C to about 30°C. The aforesaid reaction can be conducted for a period from about 1 hour to about 24 hours, preferably for about 3 hours.

Optionally, the aforesaid reaction can be effected in the presence of an acid binding agent, for example a tertiary amine (such as triethylamine), pyridine (such as 2,6-lutidine or 4-dimethylaminopyridine), or dimethylaniline. Optionally, the aforesaid reaction can also be carried out in the presence of molecular sieves, an inorganic base (such as calcium carbonate or sodium bicarbonate) or an oxirane, which binds the hydrogen gas liberated in the aforesaid reaction. The oxirane is preferably C_{1-6}alkyl-1,2-alkylene oxide, such as ethylene oxide or propylene oxide.

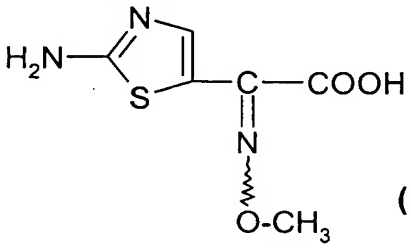
Optionally, the aforesaid reaction can be conducted in the presence of a coupling agent. Suitable coupling agents include N,N'-diethylcarbodiimide, N,N'-dipropyl carbodiimide, N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, N-ethyl-N'-[3-(dimethylamino)propyl]carbodiimide, N,N'-carbonyldiimidazole, and N,N'-carbonyldithiazole. Preferably, the coupling agent is N,N'-diethylcarbodiimide. Preferably the reaction is conducted in the absence of any couplings agents.

Optionally, the aforesaid reaction can be conducted in the presence of a catalyst. Suitable catalysts include a Lewis acid, such as boron trihalide or aluminum halide. Preferably the reaction is conducted in the absence of any catalysts.

The compound of formula **III** can be prepared by methods known in the art. Suitable methods include those described, for example, in U.K. Patent No. 2 107 307 B, U.K. Patent Specification No. 1,536,281 and U.K. Patent Specification No. 1,508,064. Preferably, the compound of formula **III** (i.e. R^2L), wherein R^2 has a formula:



wherein A^1 is 2-aminothiazol-4-yl, A^2 is methyl, and L is (C_{1-6}alkyl)sulfonyl, such as methylsulfonyl, or di(C_{1-6}alkyl)phosphorothioate, such as diethylphosphorothioate, can be prepared by reacting a compound of formula **IIIb**



(IIIb)

with (C_{1-6}alkyl)sulfonylhalide, such as methanesulfonylchloride, or di(C_{1-6}alkyl)thiophosphonic acid, such as diethylthiophoshonic acid.

Most preferably, the compound of formula **III** is diethylthiophoshoryl-[Z]-2-aminothiazol-4-yl-methoxylamino (DAMA), which can be prepared according to the methods described in U.S. Patent No. 5,567,813 and EP 628561.

Scheme 2 refers to the preparation of a compound of formula **II**. Referring to Scheme 2, a compound of formula **II** can be prepared by reacting a compound of formula **IV**, wherein R^3 is preferably para-nitrobenzyl ester; and X is preferably chloro; with a suitable deprotecting agent in a solvent.

Suitable deprotecting agents include sodium dithionite or a catalytic hydrogenating agent, such as hydrogen gas over 10% palladium on carbon.

Suitable solvents include acetone, water, tetrahydrofuran, methylene chloride or mixtures thereof. Preferably the solvent is a mixture of 3:1 acetone and water.

The aforesaid reaction can be conducted at a temperature of about 0°C to about 45°C, preferably about 45°C. The aforesaid reaction can be conducted for a period from about 1 hour to about 24 hours, preferably from about 1 hour.

A compound of formula **IV** can be prepared by various synthetic methods such as those described in the United States Non-Provisional Patent Application entitled "Process and

Ester Derivatives Useful For Preparation of Cephalosporins", filed December 4, 2001. These methods are described hereinbelow in Schemes 4-6.

Scheme 3 refers to an alternative process of preparation of a compound of formula **I**. Referring to Scheme 3, a compound of formula **I** can be prepared by reacting a compound of formula **V**, wherein R^3 is preferably allyl; with a suitable deprotecting agent in a solvent.

Suitable deprotecting agents include sodium dithionite or tetrakistriphenyl phosphine palladium (0).

Suitable solvents include acetone, water, tetrahydrofuran, methylene chloride or mixtures thereof. Preferably the solvent is methylene chloride.

The aforesaid reaction can be conducted at a temperature of about 0°C to about 45°C. The aforesaid reaction can be conducted for a period from about 1 hour to about 24 hours.

A compound of formula **V** can be prepared by reacting a compound of formula **IV**, wherein R^3 is preferably allyl; and X is preferably chloro; with a compound of formula **III**

$$R^2\text{-}L \qquad \text{(III)}$$

in a solvent.

Suitable solvents for the aforesaid reaction include methylene chloride, tetrahydrofuran or mixtures thereof. Preferably, the solvent is methylene chloride.

Optionally, the aforesaid reaction can be conducted in the presence of a coupling agent. Suitable coupling agents include N,N'-diethylcarbodiimide, N,N'-dipropyl carbodiimide, N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, N-ethyl-N'-[3-(dimethylamino)propyl]carbodiimide, N,N'-carbonyldiimidazole, or N,N'-carbonyldithiazole. Preferably, the coupling agent is N,N'-diethylcarbodiimide. Preferably the aforesaid reaction is conducted without any coupling agents.

Optionally, the aforesaid reaction can be conducted in the presence of a catalyst. Suitable catalysts include a Lewis acid, such as boron trihalide or aluminum halide. Preferably the aforesaid reaction is conducted without any catalysts.

The aforesaid reaction can be conducted at a temperature of about -40°C to about +40°C, preferably about +20°C to about +40°C. The aforesaid reaction can be conducted for a period from about 1 hour to about 24 hours; preferably about 24 hours.

A compound of formula **IV** can be prepared as described below in the description for Schemes 4-6.

Scheme 4 refers to the preparation of a compound of formula **(IV)**. Referring to Scheme 4, a compound of formula **(IV)** wherein R^1 is preferably *para*-nitrobenzyl can be prepared by reaction of a compound of formula **(VI)** wherein R^1 is preferably *para*-nitrobenzyl, and R^2 is preferably $C_{6\text{-}10}arylC_{1\text{-}6}alkyl$, such as benzyl, with an acid in a solvent. Suitable

acids include Lewis Acids, such as phosphorus pentachloride or phosphorus pentabromide, preferably phosphorus pentachloride. Suitable solvents include toluene, xylene, tetrahydrofuran, methylene chloride or acetonitrile; preferably methylene chloride. The aforesaid process can be conducted at a temperature of about -40°C to about +40°C. The aforesaid process is conducted for a period of from about 1 hour to about 24 hours.

A compound of formula **(VI)** wherein R^1 is preferably *para*-nitrobenzyl, and R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl, can be prepared by cyclizing a compound of formula **(VIIa)**, wherein R^1 is preferably *para*-nitrobenzyl; and R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl; by heating said compound of formula **(VIIa)** in a solvent.

The aforesaid process for the conversion of compounds of formula **(VIIa)** into compounds of formula **(VI)** is a so called intramolecular Wittig-type reaction and is typically conducted by heating the above compound of formula **(VIIa)**. Suitable solvents include toluene, xylene, tetrahydrofuran, methylene chloride and acetonitrile, preferably methylene chloride. The aforesaid process is conducted at a temperature of from about 40°C to about 160°C. The aforesaid process is conducted for a period of from about 1 hour to about 24 hours, preferably about 16 hours.

The aforesaid conversion of the compound of formula **(VIIa)** to the compound of formula **(IV)** can be performed as a two step process in which the compound of formula **(VI)** may be isolated but is preferably carried out as a one step reaction without isolation of the phosphorus ylide.

Compounds of formula **(VIIa)** can be prepared by the methods of Scheme 5.

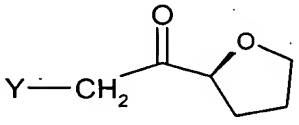
Scheme 5 refers to the preparation of compounds of the formula **(VIIa)**, wherein R^1 is preferably *para*-nitrobenzyl; and R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl; by the processes of the present invention. Compounds of the formula **(VIIa)** are intermediates useful in the preparation of compounds of formula **(IV)** in Scheme 4.

Referring to Scheme 5, the aforesaid compound of formula **(VIIa)** can be prepared by reacting a compound of formula **(VIIb)**, wherein R^1 is preferably *para*-nitrobenzyl; and R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl; and X is preferably chloro, with trimethylphoshine, in a solvent, optionally in the presence of a suitable base.

Suitable solvents include tetrahydrofuran, acetonitrile and methylene chloride, preferably tetrahydrofuran. Suitable bases include imidazole, 2,6-lutidine, pyridine, N-methylmorpholine or sodium bicarbonate, preferably sodium bicarbonate. Preferably the reaction is conducted with the suitable base during work up. The aforesaid process is conducted at a temperature of from about -40°C to about -20°C. The aforesaid process is conducted for a period of from about 30 minutes to about 1 hour.

A compound of formula **(VIIb)**, wherein R^1 is preferably *para*-nitrobenzyl; and R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl; can be prepared by reacting a compound of formula **(VIIc)**, wherein R^1 is preferably *para*-nitrobenzyl; and R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl; with a halogenating agent in the presence of a base in a solvent. Suitable halogenating agents include thionyl chloride, thionyl bromide, phosphorus tribromide or phosphorus trichloride, preferably thionyl chloride. Suitable bases include pyridine, 2,6-lutidine, N-methylmorpholine or imidazole, preferably 2,6-lutidine. Suitable solvents include tetrahydrofuran or methylene chloride, preferably methylene chloride. The aforesaid process is conducted at a temperature of from about -40°C to about -20°C, preferably about -20°C. The aforesaid process is conducted for a period of from about 15 minutes to about 1 hour, preferably about 1 hour.

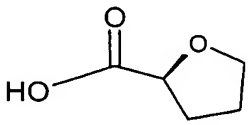
A compound of formula **(VIIc)**, wherein R^1 is preferably *para*-nitrobenzyl; and R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl; can be prepared by reacting a compound of formula **(IX)**, wherein R^1 is preferably *para*-nitrobenzyl; and R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl; with a compound of formula **(VIII)**



(VIII)

wherein Y is a leaving group such as bromo, chloro, fluoro, iodo or tosylate, preferably bromo, in a solvent. Suitable solvents include alcohol, such as methanol, ethanol and propanol; methylene chloride; acetone; dimethylformamide; or mixtures thereof. The aforesaid process is conducted at a temperature of from about 10°C to about 25°C. The aforesaid process is conducted for a period of from about 4 hours to about 24 hours.

Compounds of formula **(VIII)** are known compounds and can be prepared by standard methodology. For example, compounds of formula **(VIII)**, in which Y is chloro or bromo, can be prepared from a compound of formula **(VIIIa)**

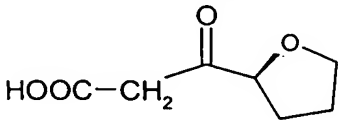


(VIIIa)

by reacting said compound of formula **(VIIIa)** with a halogenating agent, such as thionyl chloride or phophorus tribromide, to form the corresponding acid halide (such as chloroformyltetrahydrofuran or bromoformyltetrahydrofuran). Said acid halide is reacted with diazomethane to form a diazo compound. The resulting diazo compound is then treated with hydrogen chloride or hydrogen bromide to form the corresponding compound of formula **(VIII)**.

Compounds of formula **(VIIIa)**, the corresponding acid halides and diazomethane are commercially available.

Alternatively, the compound of formula **(VIII)** can be prepared *in situ* by reacting the corresponding carboxylic acid of formula **(VIIIb)**



(VIIIb)

with a halogenating agent in methanol or water solution; and subsequently exposing the solution to an acid, preferably *para*-toluene sulfonic acid. Suitable halogenating agents include bromine, chlorine or iodine, preferably bromine.

Those skilled in the art would understand that in the process of the invention, the compound of formula **(VIII)** made *in situ* is then reacted with compounds of formula **(IX)** to prepare compounds of formula **(VIIc)**, by the method described above.

Compounds of the formula **(IX)** can be prepared by the methods of Scheme 6.

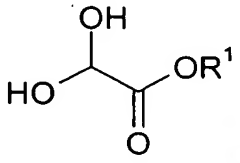
Scheme 6 refers to the preparation of compounds of the formula **(IX)**, wherein R^1 is preferably *para*-nitrobenzyl; and R^2 is preferably $C_{6\text{-}10}arylC_{1\text{-}6}alkyl$, such as benzyl; by the processes of the present invention. Compounds of the formula **(IX)** are useful intermediates in the preparation of compounds of formula **(IV)**, via compounds of the formula **(VIIa)**. The conversion of compounds of formula **(IX)** into compounds of formula I are described in Schemes 1 and 2. Referring to Scheme 6, a compound of formula **(IX)** can be prepared by reacting a compound of formula **(Xa)**, wherein R^1 is preferably *para*-nitrobenzyl; and R^2 is preferably $C_{6\text{-}10}arylC_{1\text{-}6}alkyl$, such as benzyl; with an acid in a solvent. Suitable acids include *para*-toluene sulfonic acid and methane sulfonic acid, preferably *para*-toluene sulfonic acid. Suitable solvents include methylene chloride, tetrahydrofuran, acetone or mixtures thereof, preferably methylene chloride. The aforesaid process is conducted at a temperature of from about 20°C to about 25°C. The aforesaid process is conducted for a period of from about 2 hours to about 24 hours.

A compound of formula **(Xa)**, wherein R^1 is preferably *para*-nitrobenzyl; and R^2 is preferably $C_{6\text{-}10}arylC_{1\text{-}6}alkyl$, such as benzyl; can be prepared by reacting a compound of formula **(Xb)**, wherein R^1 is preferably *para*-nitrobenzyl; and R^2 is preferably

$C_{6\text{-}10}arylC_{1\text{-}6}alkyl$, such as benzyl; with a reducing agent; in a solvent. Suitable reducing agents include sodium borohydride, sodium cyanoborohydride, borane and sodium triacetoxy borohydride, preferably sodium triacetoxyborohydride or sodium borohydride. Suitable solvents include acetic acid, methylene chloride, tetrahydrofuran, alcohol (such as isopropanol) or mixtures thereof. When the reducing agent is sodium triacetoxy borohydride,

preferably the solvent is methylene chloride. When the reducing agent is sodium borohydride, preferably the solvent is acetic acid. The aforesaid process is conducted at a temperature of from about 20°C to about 66°C. The aforesaid process is conducted for a period of from about 4 hours to about 24 hours.

Alternatively, the compound of formula **(Xa)**, wherein R^1 is preferably *para*-nitrobenzyl; and R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl; can be prepared by reacting a compound of formula **(XV)**, wherein R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl, with a compound of formula **(XIV)**,



(XIV)

wherein R^1 is preferably *para*-nitrobenzyl, in the presence of a base in a solvent. Suitable bases include diisopropylamine, triethylamine, pyridine and 2,6-lutidine; preferably triethylamine; more preferably the triethylamine is catalytic. Suitable solvents include methylene chloride, tetrahydrofuran or mixtures thereof. The aforesaid process is conducted at a temperature of from about 20°C to about 25°C. The aforesaid process is conducted for a period of from about 30 minutes to about 2 hours, preferably about 1 hour.

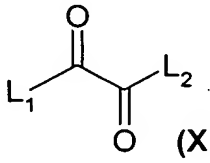
Compounds of formulae **(XIV)** and **(XV)** are individually known and are commercially available.

A compound of formula **(XIVb)**, wherein R^1 is preferably *para*-nitrobenzyl; R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl; can be prepared by reacting a compound of formula **(XII)**, wherein R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl, and said L_2 is halo, such as bromo or chloro, with a compound of formula **(XI)**

$$R^1\text{-OH} \qquad \textbf{(XI)}$$

wherein R^1 is preferably *para*-nitrobenzyl; in a solvent, in the presence of a base.

Said compound of formula **(XII)** is prepared by reacting said compound of formula **(XV)** with a compound of formula **(XIII)**



(XIII)

wherein each of L_1 and L_2 is a leaving group, such as halo, preferably chloro, in a solvent, optionally in the presence of a base. Suitable solvents include methylene chloride, tetrahydrofuran, or mixtures thereof, preferably methylene chloride. Suitable bases include diisopropylamine, triethylamine, pyridine and 2,6-lutidine, preferably triethylamine. The

aforesaid process is conducted at a temperature of about -78°C to about 25°C, preferably about -78°C. The aforesaid process is conducted for a period of from about 5 minutes to about 10 minutes, preferably about 5 minutes.

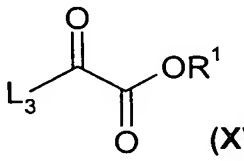
The compound of formula **(XII)** may be isolated, or may be carried on to the next step without isolation. Preferably the compound of formula **(XII)** is isolated.

Compounds of formula **(XI)** and **(XIII)** are commercially available.

Alternatively, a compound of formula **(Xb)**, wherein R^1 is preferably *para*-nitrobenzyl; and R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl; can be prepared by reacting a compound of formula **(Xc)**, wherein R^1 is preferably *para*-nitrobenzyl; R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl; R^3 is preferably $C_{1-6}alkyl$, such as methyl; and R^4 is preferably $C_{1-6}alkyl$, such as methyl; with an oxidizing agent, in a solvent. Suitable oxidizing agents include ozone. Suitable solvents include methylene chloride, tetrahydrofuran or mixtures thereof, preferably methylene chloride. The aforesaid process is conducted at a temperature of about -70°C. The aforesaid process is conducted for a period of from about 1 hour to about 24 hours.

A compound of formula **(Xc)** is commercially available.

Alternatively, a compound of formula **(Xb)**, wherein R^1 is preferably *para*-nitrobenzyl, and R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl; can be prepared by reacting a compound of formula **(XV)**, wherein R^2 is preferably $C_{6-10}arylC_{1-6}alkyl$, such as benzyl; with a compound of formula **(XVI)**



(XVI) ;

wherein R^1 is preferably *para*-nitrobenzyl, and L_3 is a leaving group, such as halo, preferably chloro, in a solvent in the presence of a base. Suitable solvents include methylene chloride, tetrahydrofuran or mixtures thereof. Suitable bases include diisopropylamine, triethylamine, pyridine or 2,6-lutidine. The aforesaid process is conducted at a temperature of from about-40°C to about 25°C. The aforesaid process is conducted for a period of about 5 minutes to 15 minutes.

Compounds of formula **(XVI)** are commercially available.

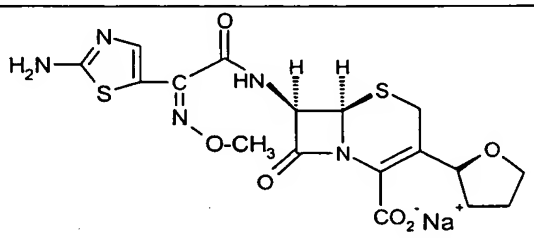
Compounds of this invention can be crystallized or recrystallized from solvents such as organic solvents. In such cases solvates can be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that can be produced by processes such as lyophilization.

The compounds of formula (I) are useful for the preparation of a 3-cyclic-ether-substituted cephalosporin, i.e., the active compound. The active compound possesses activities against gram positive and gram negative bacteria. Methods for assaying the activity and methods for formulating and administering the active compounds are disclosed in United States Patent No. 6,020,329, issued February 1, 2000. Methods of treatments are also described in the aforesaid patent.

The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (ppm) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Commercial reagents were utilized without further purification. Room or ambient temperature refers to 20°C to 25°C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure means that a rotary evaporator was used. TLC stands for thin liquid chromatography. HPLC stands for high pressure liquid chromatography. GC stands for gas chromatography.

Example 1

Sodium 7-(2-(2-aminothiazol-4-yl)-2-methoxyimino)-3-(tetrahydrofuran-2-yl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

No.	Structure	Molecular Weight
1		453.48

METHOD A: FROM 7-AMINO-8-OXO-3-(TETRAHYDROFURAN-2-YL)-5–THIA-1-AZA-BICYCLO[4.2.0]OCTA-1(6),2,4-TRIENE-2-CARBOXYLIC ACID.

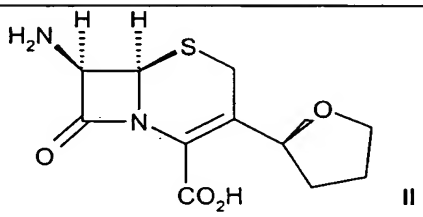
7-Amino-8-oxo-3-(tetrahydrofuran-2-yl)-5–thia-1-aza-bicyclo[4.2.0]octa-1(6),2,4-triene-2-carboxylic acid (20 g, 75 mmol), water (300 ml), acetone (400 ml), and a mixture of (Z)-2-amino-α-(methoxyimino)-4-thiazoleacetic acid anhydride and O,O-diethyl hydrogenphosphorothioate (27 g, 1.06 equivalents) were combined to form a slurry. The pH of the slurry was adjusted to between 7 to 7.5 by using aqueous sodium hydroxide. After complete dissolution was obtained, the reaction mixture was stirred for 3 hours. The product was precipitated by the addition of acetone (3200 mL). The resulting slurry was granulated, filtered, and dried under vacuo to give the title compound (29.0 g, 80%).

METHOD B: FROM ALLYL-7-(2-(2-AMINOTHIAZOL-4-YL)-2-METHOXYIMINO)-3-TETRAHYDROFURAN-2-YL)-8-OXO-5-THIA-1-AZA-BICYCLO[4.2.0]OCT-2-ENE-2-CARBOXYLATE, BENZENE SULPHINIC ACID SALT

To a 10-liter glass vessel was charged methylene chloride (4.50 liters) followed by tetrakis(triphenylphospine) palladium (9.0 g, 7.8 mmoles) in nitrogen atmosphere. Triphenylphosphine (1.0 g, 3.8 mmoles) was added and stirred into the solution. Allyl-7-(2-(2-aminothiazol-4-yl)-2-methoxyimino)-3-tetrahydrofuran-2-yl)-8-oxo-5-thia -1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate, benzene sulphinic acid salt (225.0g, 354 mmoles) was charged and warmed to 27-30°C. The reaction was monitored by HPLC, and further additions of catalyst was made as required. On completion, the solid product was filtered and washed twice with methylene chloride (700 ml total). The yellow to tan product was then air dried to achieve a constant weight before storage in a freezer. The yields range from 49-110.1%.

Example 2

7-Amino-8-oxo-3-(tetrahydrofuran-2-yl)-5-thia-1-aza-bicyclo[4.2.0]octa-1(6),2,4-triene-2-carboxylic acid

No.	Structure	Molecular Weight
2	 II	270.29

7-Amino-8-oxo-3-(tetrahydrofuran-2-yl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene -2-carboxylic acid 4-nitro-benzyl ester (20 g, 54 mmol), water (30 ml) and acetone (90 ml) were combined to form a slurry. The pH of the slurry was adjusted to 7 by using aqueous ammonia solution (15%). To the resulting solution was added sodium hydrosulfite (32 g, 3.8 equiv.) in water (40 mL) solution. The pH of the resulting solution was adjusted to 7 by using aqueous ammonia (15%) while maintaining the temperature between 40°C to 45°C. After stirring for 1 hour at 45°C, the pH was re-adjusted to 3.5 with a hydrochloric acid aqueous solution (15%). The resulting slurry was granulated, filtered and dried to afford the title compound (11.3 g, 80%).

Preparation 1: (3-Benzyl-7-oxo-4-thia-2,6-diaza-bicyclo[3.2.0]hept-2-en-6-yl)-hydroxy-acetic acid-4-nitro-benzyl ester

Isopropanol (500 mL), methylene chloride (1800 mL) and (1R)-(4-nitrophenyl)methyl ester-α,1-methylethylidene)-7-oxo-3-(phenylmethyl)-4-thia-2,6-diazabicyclo[3.2.0]hept-2-ene

-6-acetic acid (250 g) were combined and the reaction mixture cooled at -70°C. To the cooled reaction mixture, ozone was bubbled until the ozonolysis was completed. To the resulting solution, a mixture of glacial acetic acid (625 mL) and isopropanol (750 mL) was added followed by a mixture of isopropanol (100 mL), water (100 mL) and sodium borohydride (22 g). After the reduction was completed, a sodium metabisulfite in water solution was added followed by the pH adjustment to 1.5 to 2.5 with hydrochloric acid (15%). The layers were separated and the organic layer was washed twice with aqueous sodium chloride (1000 mL). The organic layer was concentrated under vacuum and the resulting slurry granulated, filtered, and the cake washed with isopropanol. The product was dried under vacuo.

Preparation 2: Hydroxy-{2-oxo-4-[2-oxo-2-(tetrahydrofuran-2-yl)-ethylsulfanyl]-3-phenylacetylamino-azetidin-1-yl}-acetic acid 4-nitro-benzyl ester

Bromine (51 g) and methanol (270 mL) were combined followed by a dropwise addition of a 1-(tetrahydro-2-furanyl)-ethanone (30 g) in methanol (30 mL) solution at 30°C. An aqueous sodium thiosulfate solution was then added followed by methylene chloride (300 mL). The layers were separated and the organic layer washed twice with an aqueous solution of sodium bicarbonate (300 mL). The resulting organic layer was concentrated followed by the addition of acetone (600 mL) and para-toluene sulfonic acid (6 g). After heating to reflux for 2 hours, the reaction was cooled and (3-benzyl-7-oxo-4-thia-2,6-diaza-bicyclo[3.2.0]hept-2-en-6-yl)-hydroxy-acetic acid 4-nitro-benzyl ester (100 g) and an additional para-toluene sulfonic acid (6 g) were charged. The resulting solution was stirred for 2 hours followed by a pH adjustment between 3 to 4 by using pyridine. The reaction was concentrated followed by the addition of water (180 mL), methylene chloride (600 mL) and hydrochloric acid (9 mL, 15%) to adjust the pH between 1 and 2. The layers were separated and the methylene chloride displaced with methanol (600 mL). Isopropanol (300 mL) was added to complete the precipitation and the resulting slurry was granulated, filtered and the cake washed with isopropanol. The product was dried under vacuo.

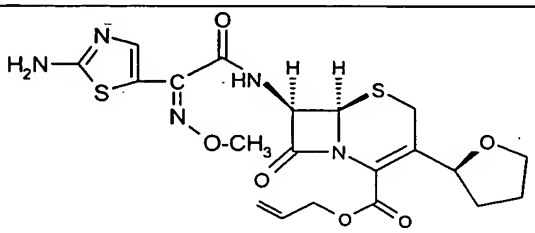
Preparation 3: 7-Amino-8-oxo-3-(tetrahydrofuran-2-yl)-5-thia-1-aza-bicyclo[4.2.0] oct-2-ene-2-carboxylic acid 4-nitro-benzyl ester

Thionyl chloride (45 ml, 0.615 mol) was added dropwise to a solution of hydroxy-{2-oxo-4-[2-oxo-2-(tetrahydrofuran-2-yl)-ethylsulfanyl]-3-phenylacetylamino-azetidin-1-yl}-acetic acid 4-nitro-benzyl ester (202 g, 0.362 mol) and 2,6-lutidine (58 ml, 0.500 mol) in dichloromethane (4 liters) at -20°C. After stirring for 1 hour, the solution was washed twice with saturated sodium chloride (1 liter) and concentrated. To the concentrated solution was added trimethylphosphine in tetrahydrofuran solution (110 ml, 3M, 330 mmol), the solution stirred for 1 hour, washed with diluted sodium hydrogen carbonate and saturated sodium chloride. After stirring at reflux for 16 hours, the solution was washed with water and saturated

sodium chloride. The solution was concentrated and cooled to -40°C followed by a dropwise addition of phosphorus pentachloride (104 g, 0.5 mol). α-Picoline (92 ml) in dichloromethane (60 ml) solution was added while maintaining the temperature between -40°C to 30°C. The mixture was stirred for 1 hour followed by the addition of isopropanol (660 ml). The reaction mixture was warmed to 22°C, granulated, filtered and dried to give the title compound (250 g, 45%).

Example 3

Allyl-7-(2-(2-Aminothiazol-4-yl)-2-methoxyimino)-3-tetrahydrofuran-2-yl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate, benzene sulphinic acid salt

No.	Structure	Molecular Weight
3		493.56 (634.62 as benzene sulphinic acid salt)

Preparation 1: Allyl-7-phenylacetamido-3-(tetrahydrofuran-2-yl)-8-oxo-5-thia-1-aza-bicyclo[4.2.0]-oct-2-ene-2-carboxylate

To a 100-liter glass vessel was added toluene (47 liters) and allyl-2-tri-n-methylphosphororanylidene-2-(3-phenylacetamido-4-(tetrahydrofuran-2 -ylcarbonyl-methylthio)azetidin-on-1yl)acetate (1990 g). The solution was purged with nitrogen and brought to reflux. Any water present was collected and the solution was refluxed for 20 hours. After sampling for TLC/HPLC analysis, the solution was cooled back to ambient temperature. The solution was then run through Silica Gel 60 (4.5 kg), with the silica being further eluted with additional toluene (33 liters). The toluene was then stripped under vacuo at a maximum temperature of 60°C. Ethyl acetate was then added and was then stripped under vacuo at a maximum temperature of 60°C. To the semi solid oil was added tert-butyl methyl ether (2.5 liters) and the solution stirred overnight. The crystalline product was filtered off and washed with further tert-butyl methyl ether (0.3 liters). The mother liquors were concentrated and resubjected to silica chromatography (dissolved in 5 liters of toluene, added onto silica, eluted with 15 liters of toluene) and crystallized in the same fashion to afford a second crop. The product was isolated as a white crystalline solid. Yields range from 70% to 80%.

Preparation 2: Allyl-2-tri-n-methylphosphoranylidene-2-(3-phenylacetamido-4-(tetrahydrofuran-2-ylcarbonyl-methylthio)azetidin-on-1-yl)acetate

The solution of allyl-2-hydroxy-2-(3-phenylacetamido-4-(tetrahydrofuran-2-ylcarbonyl-methylthio)azetidin-on-1-yl)acetate in tetrahydrofuran, which was obtained from Preparation 1 of Example 3, was further diluted with additional tetrahydrofuran (total tetrahydrofuran was 12 liters). The solution was cooled back to -20°C under nitrogen and 2,6-lutidene (654.0g, 6.09 moles) was added, followed by a dropwise addition of thionyl chloride (724.0g, 6.09 moles) at a maximum temperature of -20°C. After a thirty minute stirring, the solution was allowed to warm to -10°C and sampled for TLC. The TLC showed that the starting material was converted into allyl-2-chloro-3-(3-phenylacetamido-4-(tetrahydrofuran-2-ylcarbonyl -methylthio)azetidin-on-1-yl)acetate to completion. The precipitated compounds were then filtered off and washed further with tetrahydrofuran. The tetrahydrofuran solution was then concentrated under vacuo at a maximum temperature of 30°C, redissolved in fresh tetrahydrofuran (6 liters) and cooled back to -10°C. After stirring overnight at ambient temperature, the solution was sampled for completion, diluted with ethyl acetate (35 liters) and washed with 5% sodium bicarbonate (20 liters) and 20% saturated sodium chloride (20 liters). The ethyl acetate was then stripped under vacuo at a maximum temperature of 40°C to afford thick dark oil. The yields range from 88% to 90%.

Preparation 3: Allyl-2-hydroxy-2-(3-phenylacetamido-4-(tetrahydrofuran-2-ylcarbonyl-methylthio)azetidin-on-1-yl)acetate

To a 20-liter flask was added methylene chloride (10.0 liters), tetrahydrofuran (1.0 liter) and allyl 2-hydroxy-2-(3-benzyl-4-thia-2,6-diazabicyclo[3.2.0]hept-2-en-7-one) acetate (2016 g, 6.05 moles). To this solution was added 45% aqueous *para*-toluene sulphonic acid solution (500.0 g). After a three hour stirring the solution was sampled for completion with TLC. The solution was then transferred to a 50 liter glass separating vessel, and methylene chloride was added (5 liters) followed by water (2 liters). The separated organic phase was then washed with water (4 liters). The methylene chloride phase was then dried over sodium sulphate to afford a dry solution of allyl-2-hydroxy-2-(3-phenylacetamido-4-mercapto-azetidin-on-1-yl)acetate in methylene chloride that was then used without delay. To the above solution was added 86% of the solution of 2-bromoacetyltetrahydrofuran in methylene chloride (6.3 moles). The resultant solution was stripped under vacuo at a maximum temperature of 30°C to 50% of its volume. Pyridine (503.1 g, 6.36 moles) was added at a maximum temperature of 10°C. The solution was stirred overnight, diluted with methylene chloride (10 liters) and washed twice with water (10 liters total) then once with saturated sodium chloride (10%, 10 liter). After drying over sodium sulphate, the solution was concentrated under vacuo at a maximum temperature of 40°C to ensure dryness. The

solution was redissolved in tetrahydrofuran (5 liter) for use in the next step. If storage was required, the tetrahydrofuran solution was stored and dried before use.

Preparation: 4: 2-Bromoacetyltetrahydrofuran

To a 20-liter glass vessel was added methylene chloride (10.0 liters) followed by acetyltetrahydrofuran (838.0 g, 7.34 moles). The solution was then cooled back to -10°C and triethylamine was added (854.0g, 8.44 moles). The vessel was purged with nitrogen and trimethylsilane triflate (1713.0 g, 7.71 moles) was added dropwise at a maximum temperature of -8°C. Addition was typically complete in 45 minutes. After 15 minutes stirring, a sample was removed for TLC and GC analysis, which showed that the reaction was completed. N-bromosuccinimide (1340g, 7.53 moles) was added to the solution at a maximum temperature of -5°C over a period of approximately 45 minutes in six portions. After a 30 minute stirring, the solution was sampled for GC and TLC analysis, which showed that the reaction was completed. The solution was then transferred to a 50-liter separating vessel, and 5% sodium bicarbonate (5 liters) was added with caution. The solution was stirred and separated. The upper aqueous phase was discarded, and the methylene chloride phase was washed with water, dried over sodium sulphate, filtered and stored in a freezer before use in the next step.

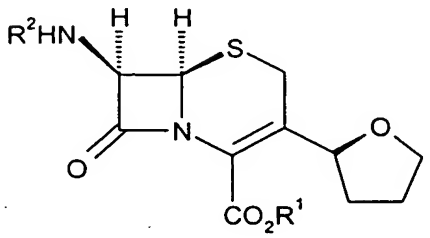
Preparation 5: Allyl-2-hydroxy-2-(3-benzyl-4-thia-2,6-diazabicyclo[3.2.0]hept-2-en-7-one)acetate

To a 50-liter glass vessel was added methylene chloride (20.6 liters) followed by 3-benzyl-4-thia-2,6-diazabicyclo[3.2.0]hept-2-en-7-one (1700 g, 7.79 moles). To this suspension was added allyl glyoxylate monohydrate (1285 g, 9.74 moles) followed by sufficient triethylamine (about 175 g) to bring the pH of the solution to 7.5-7.9. After a 1 hour stirring, the solution was sampled for TLC/HPLC analysis. Upon completion, the solution was quenched with 0.1 M of hydrochloric acid (2.75 liters) to a pH of 4.50-5.00. The upper aqueous phase was discarded, and the methylene chloride phase was washed with water (8 liters) and saturated sodium chloride (8 liters). The solution was dried over sodium sulphate and concentrated to a thick oil. The oil was dispersed in hexane (5 liters), filtered, and reslurried in tert-butyl methyl ether (5 liters) before filtration and washing with further tert-butyl methyl ether. Air drying afforded an off white crystalline product. Yields range from 72-99%.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. It is intended, therefore, that the invention be defined by the scope of the claims that follow and that such claims be interpreted as broadly as is reasonable.

CLAIMS

1. A process for preparing a 3-cyclic-ether-substituted cephalosporin of the formula I:



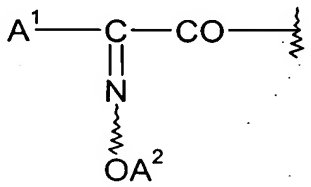
I

or a pharmaceutically acceptable salt thereof,

wherein

the group CO_2R^1 is a carboxylic acid or a carboxylate salt; and

R^2 has the formula:

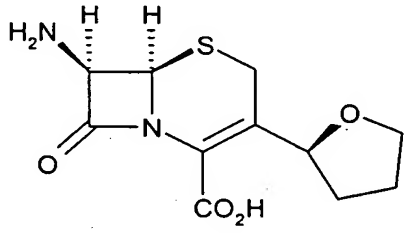


wherein

A^1 is selected from the group consisting of C_{6-10}aryl, C_{1-10}heteroaryl and C_{1-10}heterocyclyl;

A^2 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-10}aryl, C_{1-6}alkyl(CO)(C_{1-6})alkyl-O-, HO(CO)(C_{1-6})alkyl, mono-(C_{6-10}aryl)(C_{1-6}alkyl), di-(C_{6-10}aryl)(C_{1-6}alkyl), and tri-(C_{6-10}aryl)(C_{1-6}alkyl);

comprising reacting a compound of formula II:



II

with a compound of the formula III:

R^2L III;

wherein

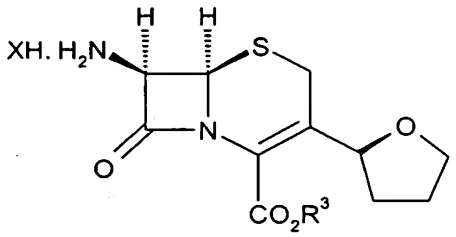
R^2 is as defined above; and

L is selected from the group consisting of hydroxy, halo, azido, mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate,

mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di(C_{1-6}alkyl)phosphorothioate, (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, (C_{1-6}alkyl)-(CO)-S-, cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy and N-oxy-succinimidyl;

in the presence of a solvent, a base, an optional coupling agent and an optional catalyst.

2. The process according to claim 1 further comprising the step of preparing said compound of formula II by reacting a compound of formula IV:

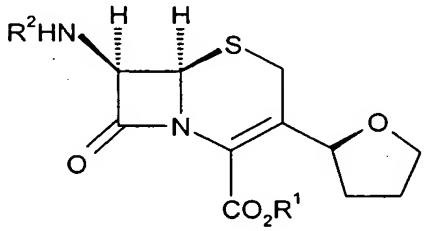


IV

wherein R^3 is para-nitrobenzyl or allyl; and X is halo;

with a suitable deprotecting agent; in the presence of a solvent.

3. A process for preparing a 3-cyclic-ether-substituted cephalosporin of the formula I:

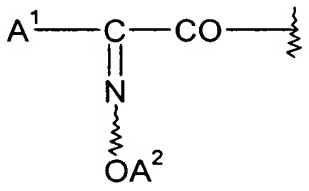


I

or a pharmaceutically acceptable salt thereof,

wherein the group CO_2R^1 is a carboxylic acid or a carboxylate salt; and

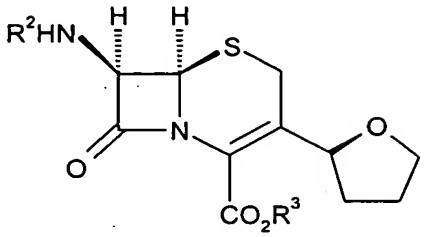
R^2 has the formula:



wherein A^1 is selected from the group consisting of C_{6-10}aryl, C_{1-10}heteroaryl and C_{1-10}heterocyclyl;

A^2 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-10}aryl, C_{1-6}alkyl(CO)(C_{1-6})alkyl-O-, HO(CO)(C_{1-6})alkyl, mono-(C_{6-10}aryl)(C_{1-6}alkyl), di-(C_{6-10}aryl)(C_{1-6}alkyl) and tri-(C_{6-10}aryl)(C_{1-6}alkyl);

comprising reacting a compound of formula **V**:

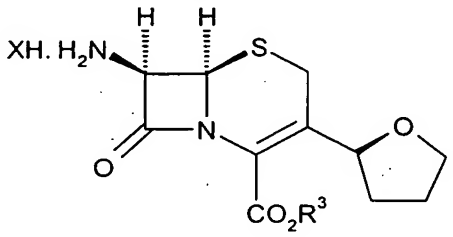


V

wherein R^2 is as defined above; and R^3 is para-nitrobenzyl or allyl;

with a suitable deprotecting agent in the presence of a solvent.

4. The process according to claim 3 further comprising preparing said compound of formula V by reacting a compound of formula IV:



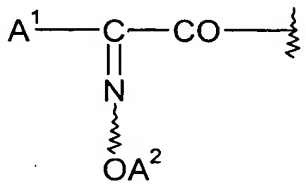
IV

wherein R^3 is para-nitrobenzyl or allyl; and X is halo;

with a compound of the formula **III**:

R^2L **III**;

wherein R^2 has the formula:



wherein A^1 is selected from the group consisting of C_{6-10}aryl, C_{1-10}heteroaryl and C_{1-10}heterocyclyl;

A^2 is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-10}cycloalkyl, C_{6-10}aryl, C_{1-6}alkyl(CO)(C_{1-6})alkyl-O-, HO(CO)(C_{1-6})alkyl, mono-(C_{6-10}aryl)(C_{1-6}alkyl), di-(C_{6-10}aryl)(C_{1-6}alkyl) and tri-(C_{6-10}aryl)(C_{1-6}alkyl); and

L is selected from the group consisting of hydroxy, halo, azido, mono(C_{1-6}alkyl)carbonate, (C_{1-6}alkyl)carboxylate, (C_{6-10}aryl)carboxylate, mono-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di-(C_{6-10}aryl)(C_{1-6}alkyl)carboxylate, di(C_{1-6}alkyl)phosphorothioate, (C_{1-6}alkyl)sulfonyl, mono-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, di-(C_{1-6}alkyl)(C_{6-10}aryl)sulfonyl, (C_{1-6}alkyl)-(CO)-S-, cyano-C_{1-6}alkoxy, C_{6-10}aryloxy, 3-benzthiazolyloxy, 8-quinolinyloxy and N-oxy-succinimidyl;

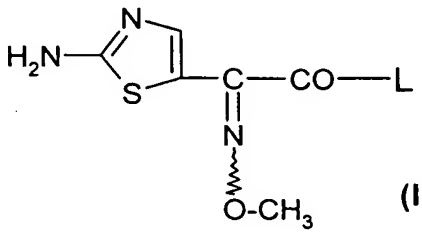
in the presence of a solvent.

5. The process according to claim 1, wherein said A^1 moiety of said R^2 is C_{1-10}heteroaryl selected from the group consisting of furyl, thienyl, pyridyl, aminothiazolyl and aminothiadiazolyl, wherein said amino moiety of said aminothiazolyl or aminothiadiazolyl is optionally protected.

6. A process according to claim 1, wherein said A^2 moiety of said R^2 is C_{1-6}alkyl.

7. A process according to claim 1, wherein L of said compound of the formula **III** is selected from the group consisting of halo, methanesulfonyl, diethylphosphorothioate and 3-benzthiazolyloxy.

8. A process according to claim 1, wherein said compound of formula **III** has a formula **IIIa**:



(IIIa)

and wherein L is selected from the group consisting of halo, methanesulfonyl, diethylphosphorothioate and 3-benzthiazolyloxy.

9. A process according to claim 1, wherein said solvent is water, acetone, tetrahydrofuran, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, methylene chloride, 1,2-dichloroethane or mixtures thereof.

10. A process according to claim 1, wherein said solvent is water, acetone, or mixtures thereof.

11. A process according to claim 1, wherein a catalyst is used.

12. A process according to claim 11 wherein said catalyst is a Lewis acid catalyst selected from the group consisting of boron trihalide and aluminum halide.

13. A process according to claim 1 wherein said base is diisopropylethylamine or sodium hydroxide.

14. A process according to claim 1, wherein said coupling agent is selected from the group consisting of N,N'-diethylcarbodiimide, N,N'-dipropyl carbodiimide, N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, N-ethyl-N'-[3-(dimethylamino)propyl]carbodiimide, N,N'-carbonyldiimidazole and N,N'-carbonyldithiazole.

15. A process according to claim 1, wherein said coupling agent is N,N'-dicyclohexylcarbodiimide.

16. A process according to claim 1, wherein said X is chloro.

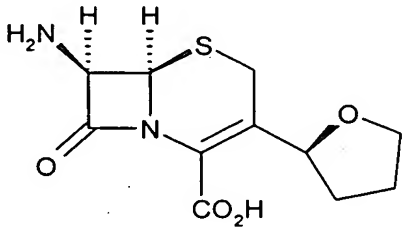
17. A process according to claim 2, wherein said R^3 is para-nitrobenzyl and said suitable deprotecting agent is sodium dithionite or a catalytic hydrogenating agent.

18. A process according to claim 2, wherein said R^3 is allyl and said suitable deprotecting agent is tetrakis triphenylphosphine palladium (0).

19. A process according to claim 17, wherein said solvent is acetone, water, tetrahydrofuran or mixtures thereof.

20. A process according to claim 4, wherein said solvent is methylene chloride, tetrahydrofuran or mixtures thereof.

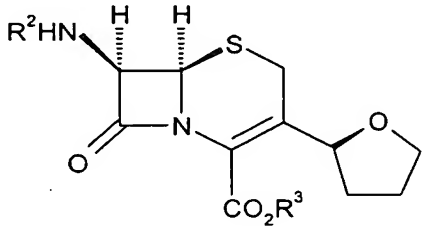
21. A compound of formula **II**:



II.

22. The compound according to claim 21 wherein said compound of the formula **II** has an enantiomeric or diastereomeric purity of 96% to 100%.

23. A compound of formula **V**:



V;

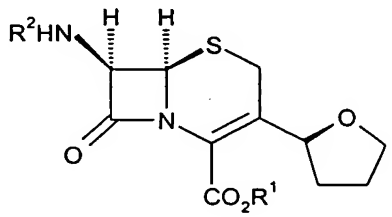
wherein R^2 is acyl; and R^3 is para-nitrobenzyl or allyl.

24. The compound according to claim 23 wherein said compound of the formula **V** has an enantiomeric or diastereomeric purity of 96% to 100%.

COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS

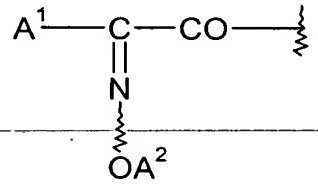
Abstract of the Invention

This invention relates to a novel process for the preparation of 3-cyclic-ether-substituted cephalosporins of formula **I**



I

wherein the group CO_2R^1 is a carboxylic acid or a carboxylate salt and R^2 has the formula:

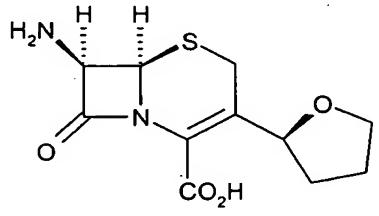


wherein

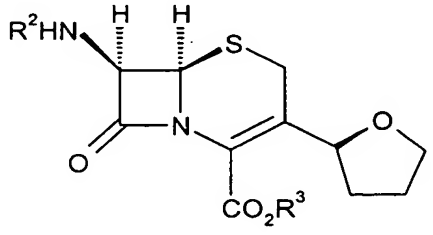
A^1 is selected from the group consisting of $C_{6\text{-}10}$aryl, $C_{1\text{-}10}$heteroaryl and $C_{1\text{-}10}$heterocyclyl;

A^2 is selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, $C_{3\text{-}10}$cycloalkyl, $C_{6\text{-}10}$aryl, $C_{1\text{-}6}$alkyl(CO)($C_{1\text{-}6}$)alkyl-O-, HO(CO)($C_{1\text{-}6}$)alkyl, mono-($C_{6\text{-}10}$aryl)($C_{1\text{-}6}$alkyl), di-($C_{6\text{-}10}$aryl)($C_{1\text{-}6}$alkyl) and tri-($C_{6\text{-}10}$aryl)($C_{1\text{-}6}$alkyl);

from a zwitterionic compound of formula **II**; or from a compound of formula **V**:



II ;



V ;

wherein R^2 is as defined above and R^3 is para-nitrobenzyl or allyl.

The invention also relates to the preparation of the above compounds of formulae **II** and **V**.